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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number
WO 02/32904 A1

(51) International Patent Classification⁷: C07D 491/20,
487/20, 498/22, 498/20, A61K 31/55, A61P 35/02 //
(C07D 491/20, 317:00, 223:00, 209:00) (C07D 487/20,
223:00, 209:00) (C07D 498/22, 317:00, 313:00, 267:00,
209:00)

(21) International Application Number: PCT/IB00/01593

(22) International Filing Date: 17 October 2000 (17.10.2000)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

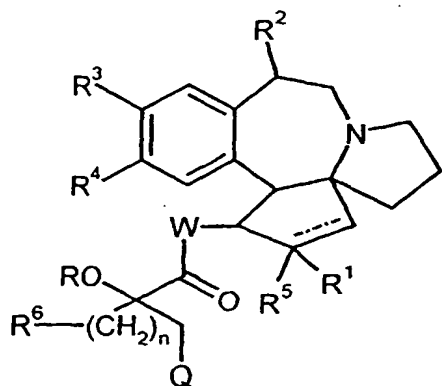
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW CEPHALOTAXANES, THEIR METHOD OF PREPARATION AND THEIR USE IN TREATMENT OF CANCERS, LEUKEMIAS, PARASITES INCLUDING THUS RESISTANT TO USUAL CHEMOTHERAPEUTIC AGENTS AND AS REVERSAL AGENTS



(I)

(57) Abstract: The present invention concerns a compound of formula (I) wherein: W represents O or NH, Q represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s), R¹ is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or null and R² is H or OH, or R¹, R² form together -O-, R³=R⁴=OMe or R³ and R⁴ form together -OCH₂O-, R is H, C₁-C₃₀alkyl or O-protecting group and R⁶ represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s), or R and R⁶ form together -CMe₂-, n is 0 to 8, R⁵ is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or O-aryl, the dotted line is null or forms a double bond depending on the meaning of R¹. It also concerns their methods of preparation and their use in treatment of cancers,

leukemias, parasites and as reversal agents of harringtonines.

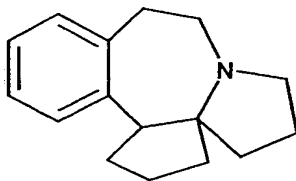
WO 02/32904 A1

TITLE : NEW CEPHALOTAXANES, THEIR METHOD OF PREPARATION AND THEIR USE IN TREATMENT OF CANCERS, LEUKEMIAS, PARASITES INCLUDING THUS RESISTANT TO USUAL CHEMOTHERAPEUTIC AGENTS AND AS REVERSAL AGENTS

5

The present invention concerns new cephalotaxanes, their methods of preparation and their use in treatment of cancers, leukemias, parasites including thus resistant to usual chemotherapeutic agents and as reversal agents of harringtonines.

10 Cephalotaxanes (CTX) are particular alkaloids today only extracted from the Cephalotaxaceae family which exhibiting the structural formula 1.



1

Several substituents may be encountered on this core: hydroxyl, ether, acyloxy etc. Some double bond or intramolecular bridge achieve to definite cephalotaxanes. Several dozen of cephalotaxanes have been isolated from various cephalotaxus species.

Cephalotaxoids include cephalotaxanes and unnatural analogs of cephalotaxanes.

20 Cephalotaxines 2 are cephalotaxanes without acyloxy side-chain.

Harringtonines (i.e. harringtonine = HA and homoharringtonine = HHT) are natural esters of cephalotaxines exhibiting generally a strong cytotoxic activity

Harringtonines are natural esters of cephalotaxines exhibiting generally a strong cytotoxic activity.

25 Harringtonoids include harringtonines and unnatural analogs of harringtonines.

Two harringtonines are very promising drugs in the treatment of certain leukemia such as Chronic Myelogenous Leukemia (CML). Definite activity of HHT was observed in acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), and myelodysplastic syndrome (MDS) (Warrell Jr Rpet al, 3:617-

621, 1985; Feldman E et al, Leukemia 6:1185-88, 1992; Feldman EJ et al, Leukemia 10:40-42, 1996; Kantarjian H et al., Cancer 63:813-817, 1989; Kantarjian H et al., J Clin Oncol 18:3513-3521, 2000). The present applicant have initiated in France compassionate use of HHT in CML patients resistant or not
5 eligible to all existing therapies and several phase II and III clinical trials including in patient with CML and AML are ongoing in France and in the U.S. However, it should be pointed out that harringtonines pertain to the series of natural drugs exhibiting the multiresistance phenomenon which led to relapse of the cancer diseases. This situation is a serious limitation to the use of natural
10 chemotherapeutic agents in the treatment of cancers and leukemia.

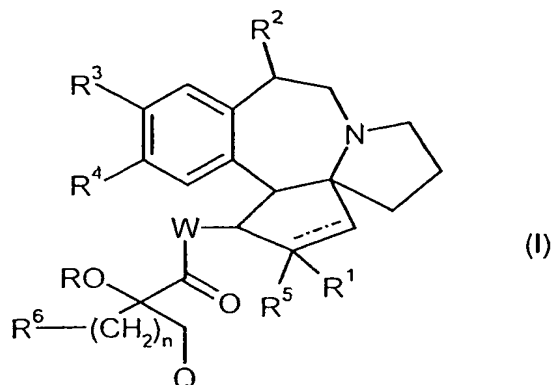
Harringtonine inhibit protein synthesis at the level of elongation, however ultimate mechanism of action of harringtonine remain unknown. The final result is the self-destruct of the cell. Clinically, harringtonines have a selective action in leukemia of the myeloid series. In addition, harringtonines interacts with P
15 Glycoprotein (PGP) and Multiresistance Protein (MRP). PGP, MRP and other efflux pumps are complex molecular entities which are ubiquitous in nature. Their role is to selectively efflux the environmental natural toxic agents, including agents of chemotherapy (anthracyclines, taxanes, epipodophyllotoxins, harringtonine, etc.) It was pointed out that no common structural feature of this natural cytotoxic
20 may related to molecular recognizing by PGP.

A number of analogs all less active than harringtonines have been synthesized. The more active among these esters are about one magnitude less cytotoxic than harringtonines in vitro (i.e. HA, HHT neoharringtonine, have an activity = IC₅₀ ranged from 10 to 30 ng per mL, whereas analog previously
25 synthesized have an IC₅₀ higher than 100ng/mL). No relation structure activity relationship had been previously found since the discovering of harringtonines.

Therefore, there is the need of new analogs of harringtonines having the same magnitude of cytotoxicity than harringtonines in vitro.

Surprisingly, the present applicant have synthesized a series of CTX
30 analogs exhibiting stronger in vitro inhibition of leukemic cell lines such as K562, than HHT used as reference.

The present invention provides cephalotaxanes having formula (I)



wherein

- W represents O or NH
 - Q represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s),
 - R¹ is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl, O-(C₃-C₃₀)cycloalkyl or null and R² is H or OH, or R¹, R² form together -O-,
 - R³ = R⁴ = OMe or R³ and R⁴ form together -OCH₂O-,
 - R is H, C₁-C₃₀alkyl or O-protecting group and R⁶ represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s), or R and R⁶ form together -CMe₂-,
 - n is 0 to 8,
 - R⁵ is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl, O-(C₃-C₃₀)cycloalkyl or O-aryl,
 - the dotted line is null or forms a double bond depending on the meaning of R¹,
- except for compounds where
- W represents O, the dotted line forms a double bond, R¹ is null, R² is H, R³ and R⁴ represent -O-CH₂-O-, R⁵ is OMe, Q = CO₂R⁷ and
 - 1°) R = H, R⁶ = -(C-OH)Me₂, n = 2 or 3, R⁷ = Me or H,
 - 2°) R = H, R⁶ = -(C-H)Me₂, n = 2 to 4, R⁷ = Me,
 - 3°) R = H, R⁶ = -(C-H)Me₂, n = 1 or 2, R⁷ = H,

4°) $R = H$, $R^6 = Ph$, $n = 1$ to 3 , $R^7 = Me$,

5°) $R = H$, $R^6 = -CH=CH-Ph$, $n = 0$, $R^7 = Me$,

6°) $R = H$, $R^6 = CH_3$, $n = 4$, $R^7 = Me$,

7°) R and R^6 form together $-CMe_2-$, $n = 2$ or 3 , $R^7 = Me$,

- 5 • W represents O , the dotted line forms a double bond, R^1 is null, R^2 is OH , R^3 and R^4 represent $-O-CH_2-O-$, R^5 is OMe and
 $R = H$, $R^6 = -(C-H)Me_2$, $n = 2$ or 3 , $R^7 = Me$
- W represents O , the dotted line is null, R^1 and R^2 represent $-O-$, R^3 and R^4
represent $-O-CH_2-O-$, R^5 is OMe and
10 $R = H$, $R^6 = -(C-H)Me_2$, $n = 2$, $R^7 = Me$.

The term "O-Protecting group" as used in the present invention refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene,
15 "Protective Groups In Organic synthesis", (John Wiley & Sons, New York (1981)).
O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl, tetrahydropyranyl ethers, substituted ethyl ethers, for example, 2,2,2-trichloroethyl, silyl ethers, for example,
20 trimethylsilyl, t-butyl dimethylsilyl and t-butyl diphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid for example, acetate, propionate, benzoate and the like.

The term " C_1 - C_{30} alkyl" as used in the present invention refers to straight or branched chain substituted or unsubstituted alkyl radicals containing from 1 to 30
25 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl and the like.

The term " C_2 - C_{30} alkenyl" as used in the present invention refers to straight or branched chain substituted or unsubstituted alkenyl radicals containing from 1 to 30 carbon atoms including, but not limited to, ethenyl, propenyl, butenyl,
30 pentenyl, hexenyl and the like.

The term "aryl" as used in the present invention refers to a monocyclic or bicyclic carbocyclic ring system having one or more aromatic rings including, but

not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like. Aryl groups can be unsubstituted or substituted with one or more substituents.

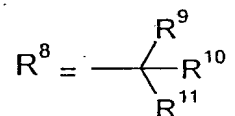
The term "aryl(C₁-C₃₀)alkyl" as used in the present invention refers to an aryl group such as defined above appended to a C₁-C₃₀alkyl radical such as defined
5 above, for example, benzyl and the like.

The term "C₃-C₃₀cycloalkyl" as used herein refers to a carbocyclic ring having 3 to 30 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. Cycloalkyl groups can be unsubstituted or substituted with one or more substituents.

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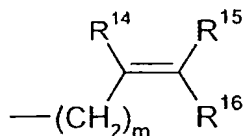
An advantageous embodiment provides compounds of formula (I) wherein

- Q = COZ-R⁸,
- Z = O, S, or NH, and



15 or Z-R⁸ is NR¹²R¹³, R¹² and R¹³ representing respectively R⁹ and R¹⁰,

R⁹, R¹⁰, R¹¹ are independently H, C₁-C₃₀alkyl, C₃-C₃₀cycloalkyl, aryl, aryl-(C₁-C₃₀)-alkyl, C₂-C₃₀alkenyl, C₂-C₃₀alkynyl, C₁-C₃₀trihalogenoalkyl, C₁-C₃₀alkylamino-(C₁-C₃₀)-alkyl, C₁-C₃₀dialkylamino-(C₁-C₃₀)-alkyl, or amino-(C₁-C₃₀)-alkyl, or



20 where R¹⁴, R¹⁵, R¹⁶ are independently H, halogen, C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, aryl, aryl-(C₁-C₃₀)-alkyl, C₂-C₃₀ alkenyl or C₂-C₃₀ alkynyl, C₁-C₃₀ trihalogenoalkyl, m is 0 to 4,

each of these groups including or not heteroatom(s), such as in particular S, N or O.

25

The term "C₂-C₃₀alkynyl" as used in the present invention refers to straight or branched chain substituted or unsubstituted alkynyl radicals containing from 1

to 30 carbon atoms including, but not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl and the like.

The term "C₁-C₃₀trihalogenoalkyl" as used in the present invention refers to straight or branched chain alkyl radicals containing from 1 to 30 carbon atoms
5 substituted by three halogen atoms.

The term "C₁-C₃₀alkylamino" as used in the present invention refers to R¹⁸NH- wherein R¹⁸ is a C₁-C₃₀alkyl group such as defined above.

The term "C₁-C₃₀dialkylamino" as used herein refers to R¹⁹R²⁰N- wherein R¹⁹ and R²⁰ are independently selected from C₁-C₃₀alkyl such as defined above.

10 The term "C₁-C₃₀aminoalkyl" as used herein refers to a C₁-C₃₀alkyl radical such as defined above to which is appended an amino group (-NH₂).

The term "C₁-C₃₀alkylamino-(C₁-C₃₀)-alkyl" as used herein refers to a C₁-C₃₀alkyl radical such as defined above to which is appended an C₁-C₃₀alkylamino group such as defined above.

15 The term "C₁-C₃₀dialkylamino-(C₁-C₃₀)-alkyl" as used herein refers to a C₁-C₃₀alkyl radical such as defined above to which is appended an C₁-C₃₀dialkylamino group such as defined above.

Another advantageous embodiment provides compounds of formula (I) wherein :

- 20 • R⁶ = -(C-Y)Me₂, -CH=CMe₂, or an aryl group
or R and R⁶ form together -CMe₂-,
Y = H, OH or halogen.

A further advantageous embodiment provides compounds of formula (I)
25 wherein .

- the dotted line forms a double bond
- R¹ is null
- R² is H
- R³ and R⁴ represent -O-CH₂-O-
- 30 • R⁵ is OMe.

A further aspect of the invention provides compounds of formula (I) wherein:

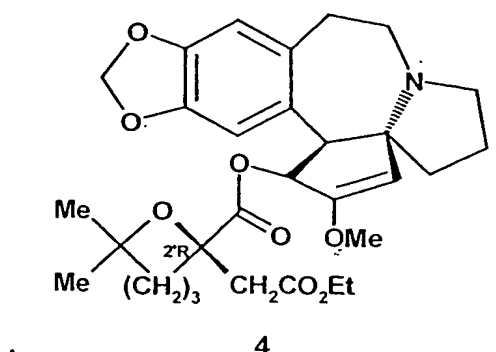
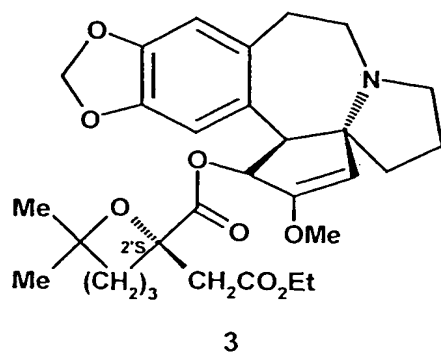
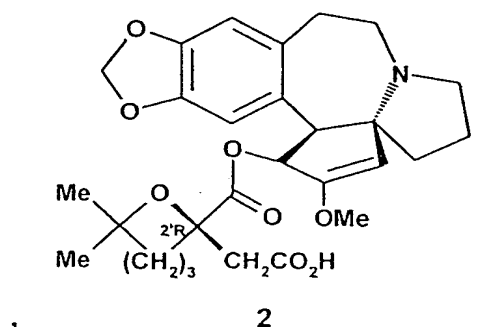
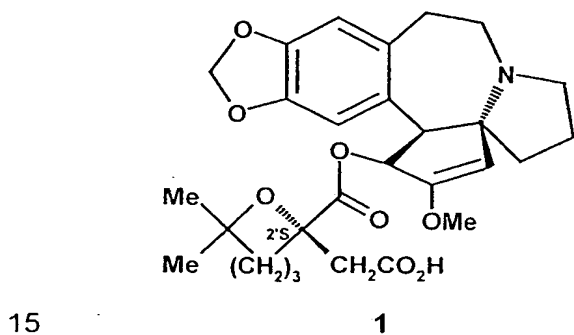
- the dotted line is null
- R^1 and R^2 represent $-O-$
- R^3 and R^4 represent $-O-CH_2-O-$
- R^5 is OMe.

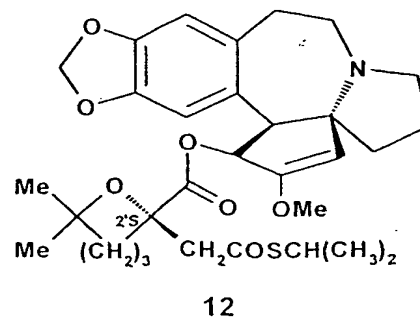
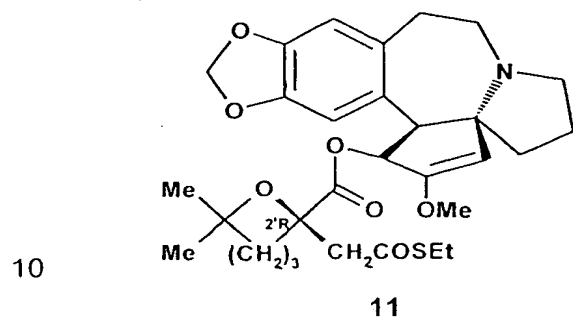
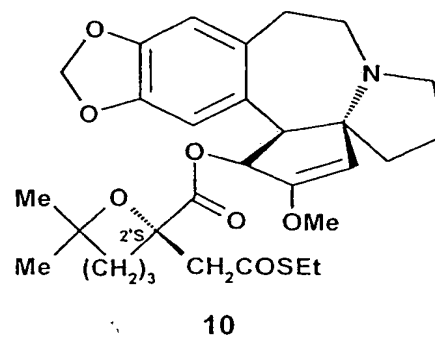
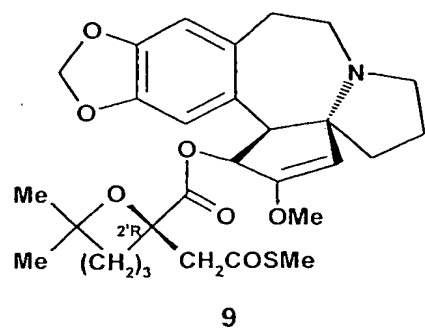
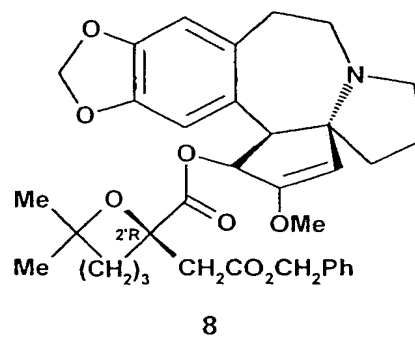
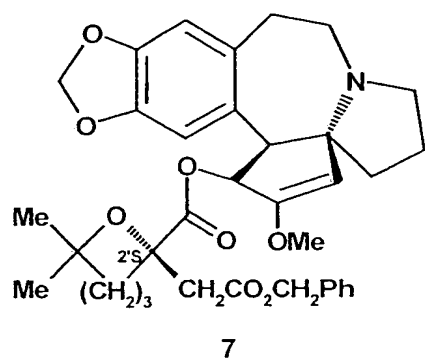
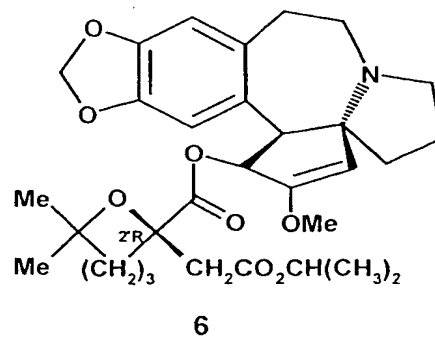
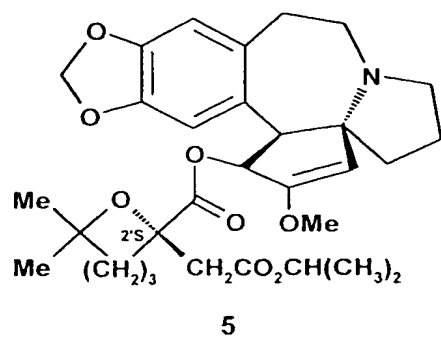
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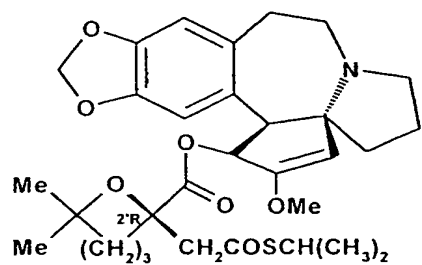
Yet, a further preferred embodiment provides compounds of formula (I) wherein n = 1 to 3.

Another further aspect of the invention provides compounds of formula (I)
10 wherein W represents O.

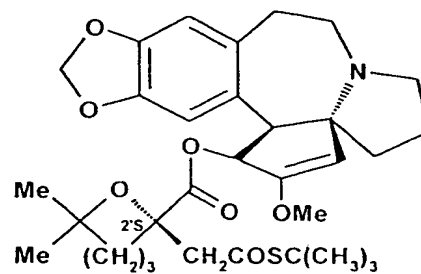
Advantageously, a compound according to the present invention is selected from the group consisting of the following compounds 1 to 65 :



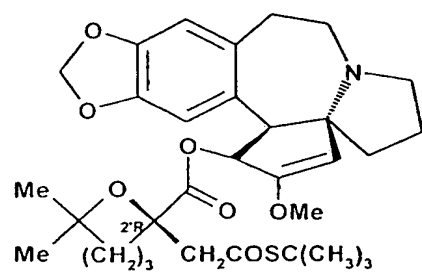




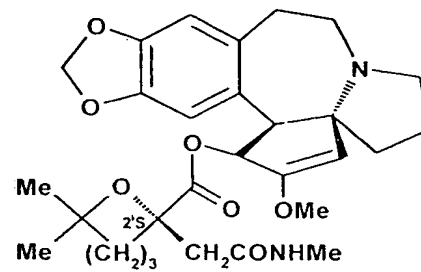
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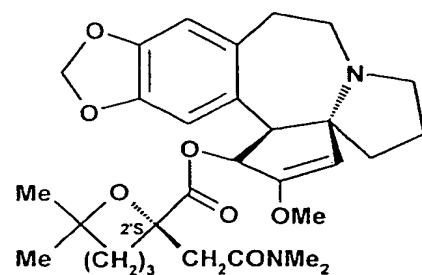
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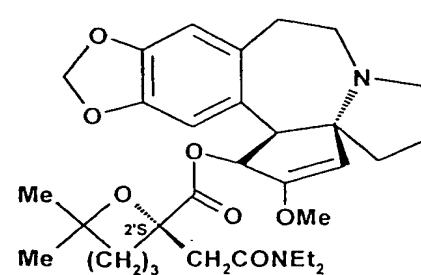
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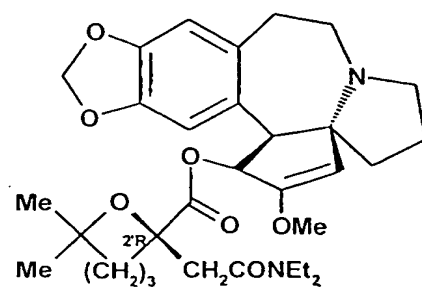
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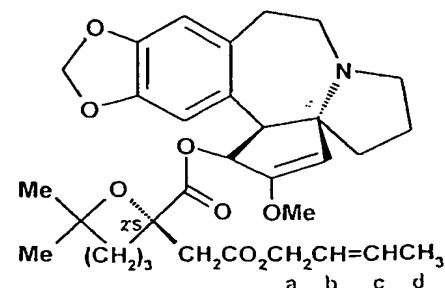
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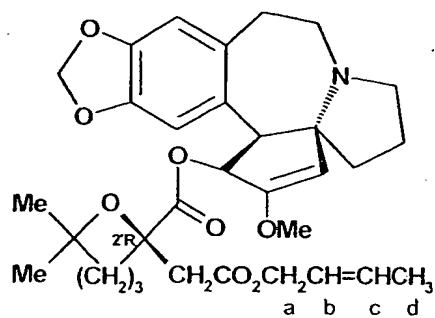
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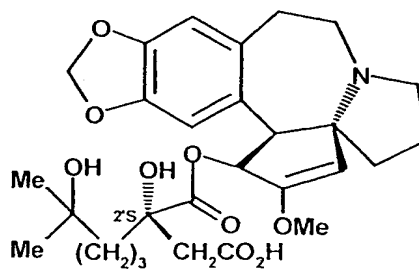
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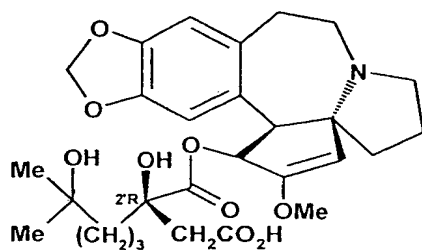
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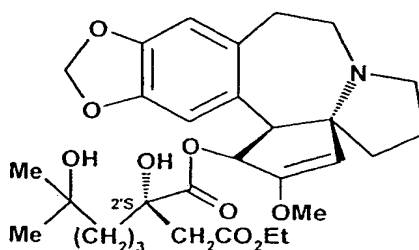
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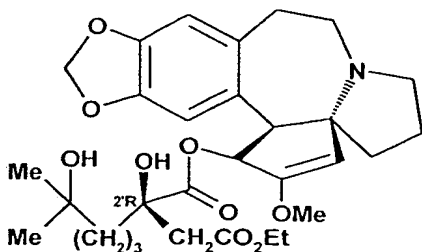
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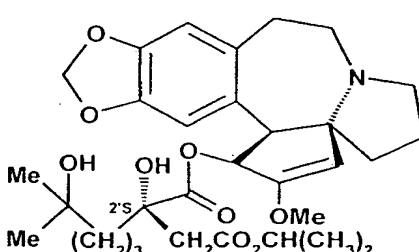
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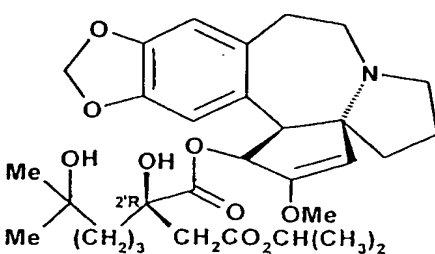
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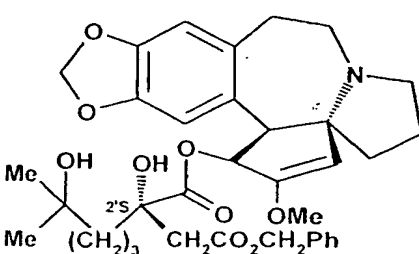
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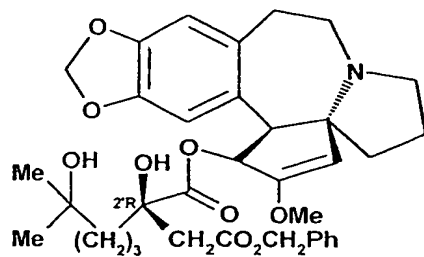
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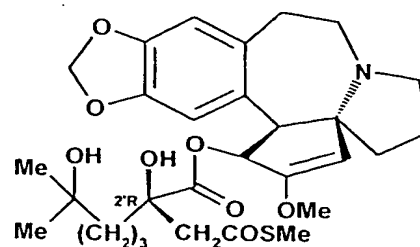
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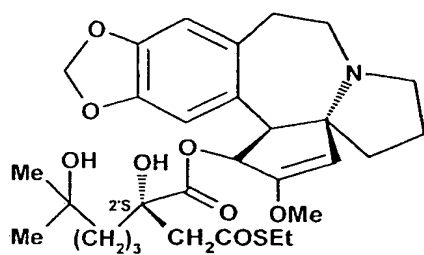
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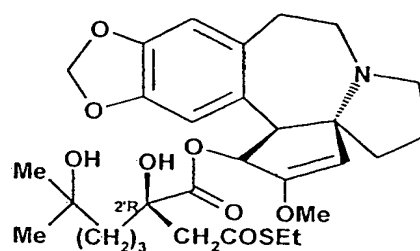
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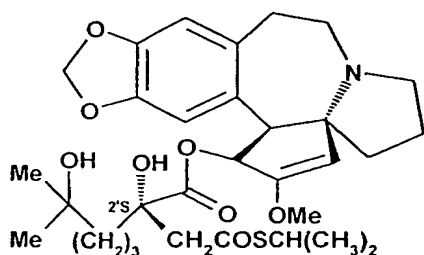
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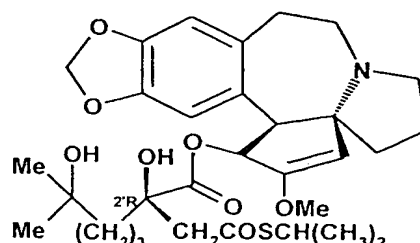
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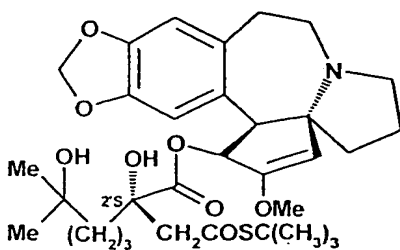
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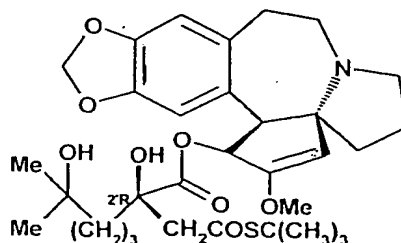
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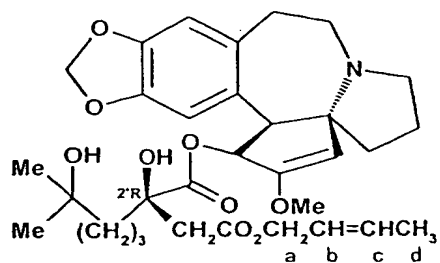
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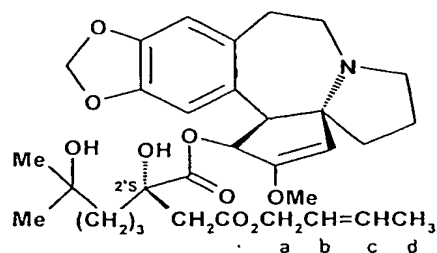
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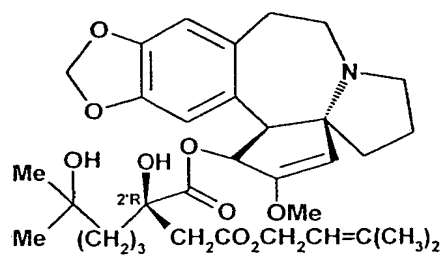
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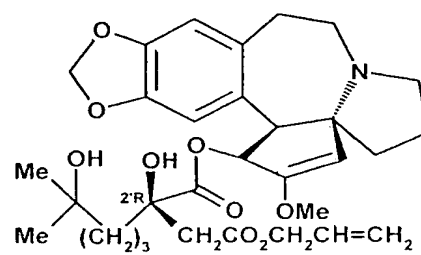
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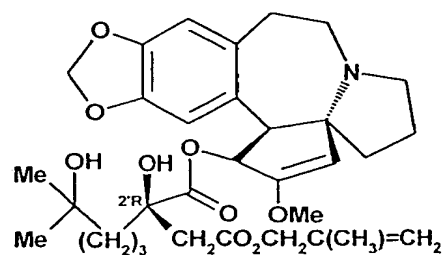
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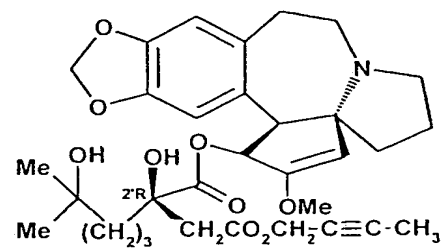
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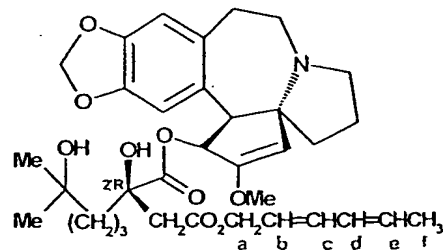
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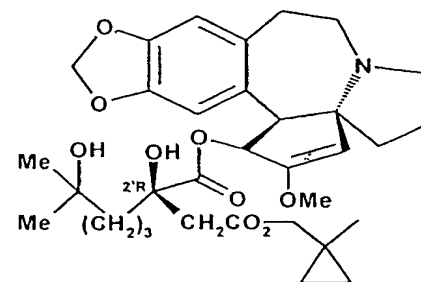
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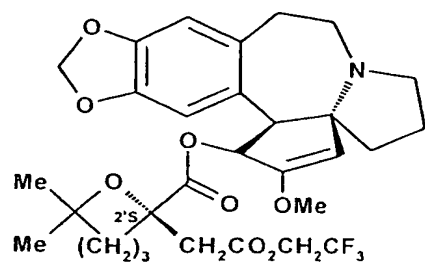


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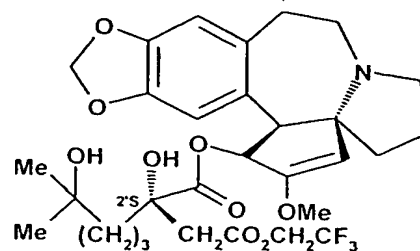


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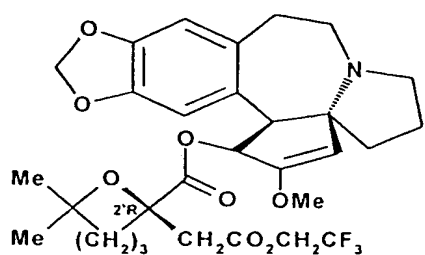
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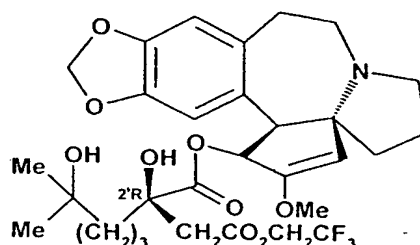
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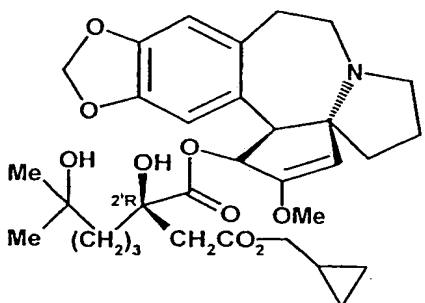
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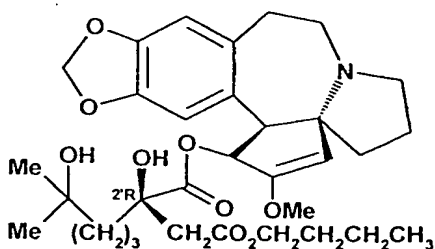
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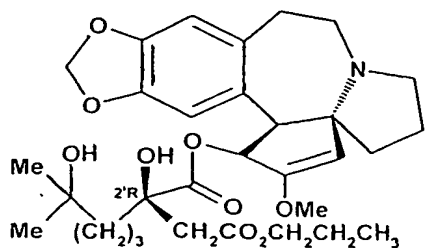
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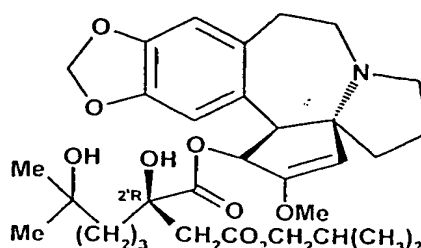
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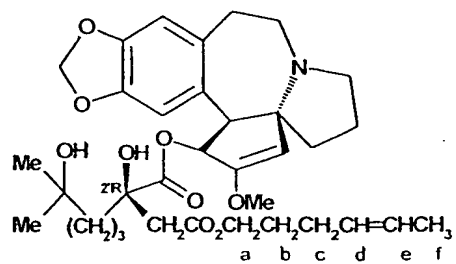
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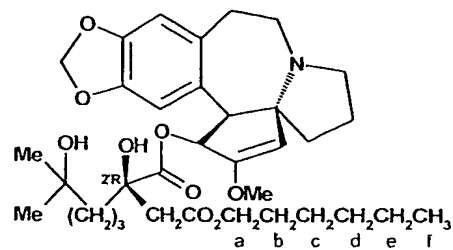
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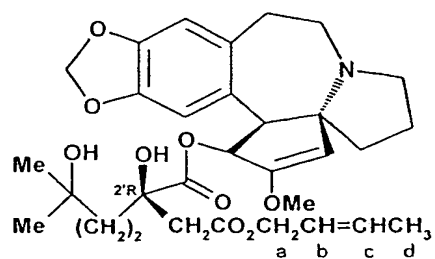
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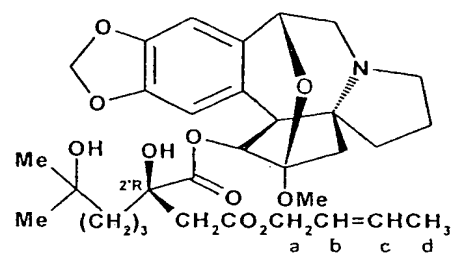
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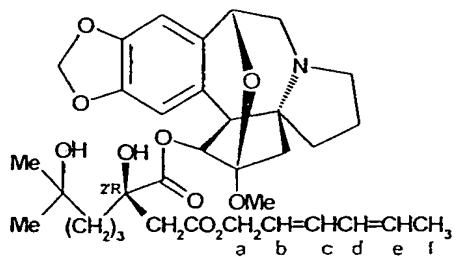
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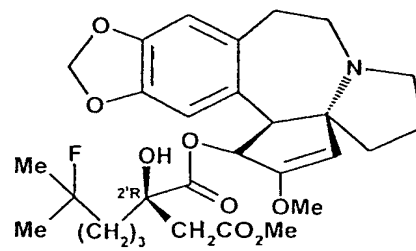
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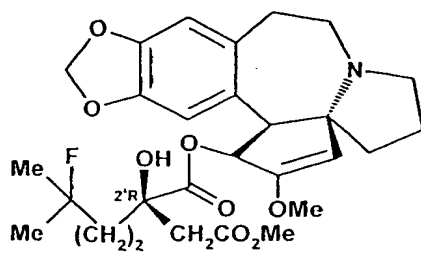
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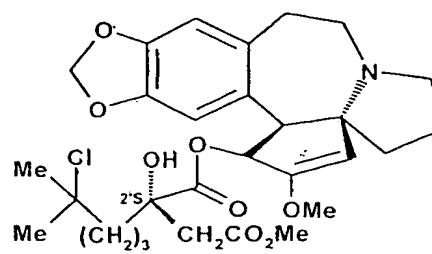
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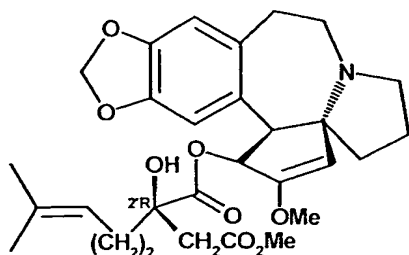
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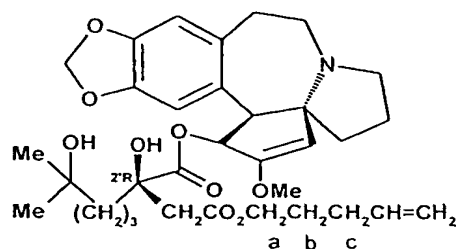
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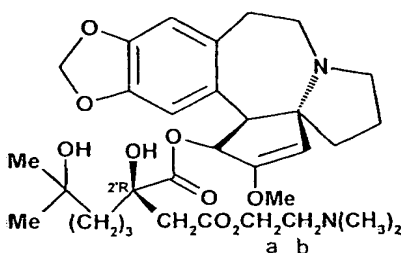
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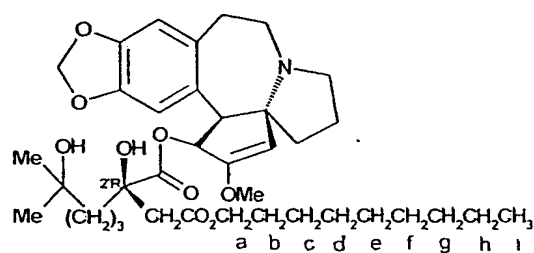
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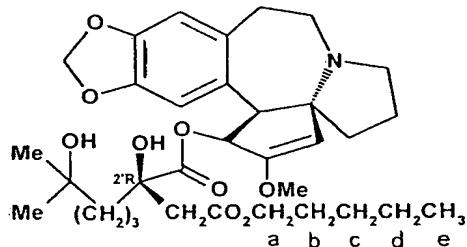


63



64

and



65.

10 Th advantageous compounds of the present invention are the one of formula (I) wherein Q represents COZR⁸, Z is such as described above and R⁸ has 6 carbon atoms without any hydrophilic group.

Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to diastereoisomers and optical isomers. The present invention is meant to comprehend such possible isomers or

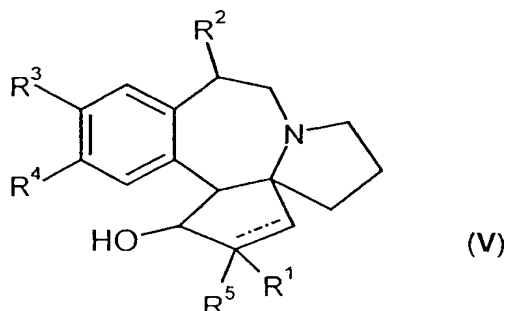
15 diastereoisomers alone or in a mixture, such as for example their racemic mixture.

Some of the compounds described herein contain olefinic double bonds and are meant to include both E and Z geometric isomers.

Another aspect of the invention is a process for preparing a compound of formula (I).

5 A. In the case where W represents NH, it comprises the following steps A1 to A2:

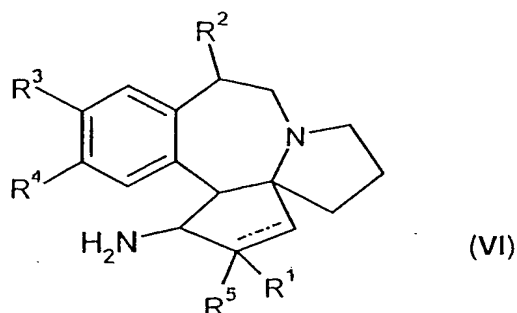
A1 : reacting cephalotaxines of formula V :



wherein

- R¹ is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl,
10 O-(C₃-C₃₀)cycloalkyl or null and
R² is H or OH, or R¹, R² form together -O-,
- R³ = R⁴ = OMe or R³ and R⁴ form together -OCH₂O-,
- R⁵ is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl,
O-(C₃-C₃₀)cycloalkyl or O-aryl,
- 15 • the dotted line is null or forms a double bond depending on the meaning of R¹

by methods known by the one skilled in the art to obtain the compounds of formula VI



20 wherein

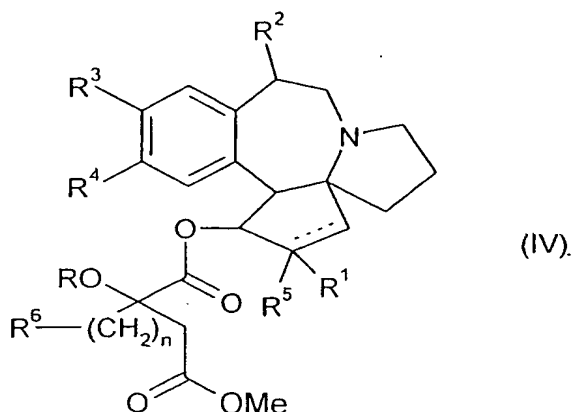
- R^1 is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl, O-(C₃-C₃₀)cycloalkyl or null and R^2 is H or OH, or R^1 , R^2 form together -O-,
- $R^3 = R^4 = \text{OMe}$ or R^3 and R^4 form together -OCH₂O-,
- 5 • R^5 is H, OH, OMe, O-(C₁-C₃₀)alkyl, O-aryl(C₁-C₃₀)alkyl, O-(C₂-C₃₀)alkenyl, O-(C₃-C₃₀)cycloalkyl or O-aryl,
- the dotted line is null or forms a double bond depending on the meaning of R^1

For example, such methods are the following :

- 10 - substituting the hydroxyl group of the cephalotaxines of formula V by an halogen or a tosylate by methods known by the one skilled in the art (such as by using SOCl₂), then substituting the halogen or the tosylate by the group NH₂ by methods known by the one skilled in the art (such as 1) the use of gaseous ammoniac in methylene chloride at 0°C and 1 atm or 2) the use of NaN₃ in DMF
- 15 followed by 2₁) a catalytic hydrogenolysis with for example Pd/C as the catalyst or 2₂) the use of LiAlH₄) to obtain the compounds of formula VI.

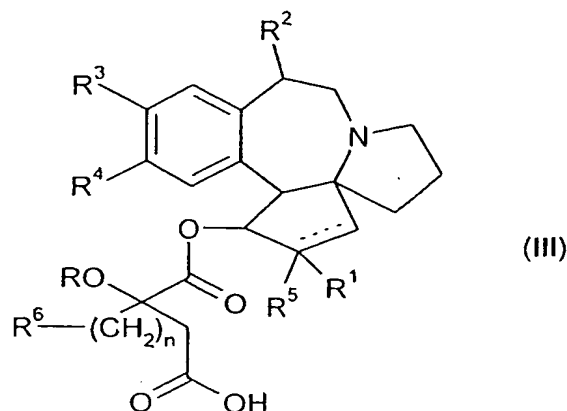
A2 : reacting the compounds of formula VI by the methods disclosed in WO 99/48894.

- 20 B. In the case where W represents O, Q = COR⁸ and R⁸ is such as described above, it comprises the step of reacting harringtonines or homoharringtonines commercially available (by SIGMA) with organometallic compounds, advantageously organolithium or grignard reagent.
- 25 C. In the case where W represents O, Q=CH₂ZR⁸ or CH₂R⁸ and Z and R⁸ are such as described above, it comprises the step of reducing harringtonines or homoharringtonines commercially available (by SIGMA) with an hydride, advantageously boron or aluminium hydride
- D. In the case where W represents O, Q = COZ-R⁸ and Z and R⁸ are such as described above, it comprises the following steps i) then ii),
- 30 i) hydrolyzing selectively the compound of formula (IV) which is available commercially



wherein

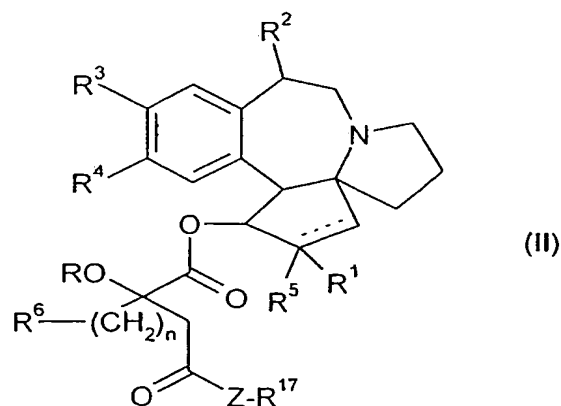
- R^1 is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl -(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or null and
- 5 R^2 is H or OH, or R^1 and R^2 form together -O-
- $R^3 = R^4 = \text{OMe}$ or R^3 and R^4 form together -OCH₂O-
- R is H, C₁-C₃₀alkyl or O-protecting group and R^6 represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms,
- 10 including or not heteroatom(s), or R and R^6 form together -CMe₂-
- n is 0 to 8.
- R^5 is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or O-aryl.
- the dotted line is null or forms a double bond depending on the meaning of R^1 ,
- 15 with an agent such as mineral hydroxide, advantageously lithium, potassium or sodium hydroxide, in hydro-organic solvent mixture to give as reaction product, amphoteric acid of formula (III)



wherein R^1 to R^5 , R and R^6 are defined as above,

- ii) performing the esterification of the above obtained amphoteric acid of formula (III) with an esterification agent and a compound of formula R^8-ZH , R^8 and Z being defined as above
- 5 and wherein the steps i) and ii) are carried out successively or simultaneously.

Advantageously the compounds of the following formula (II) :



10 wherein

- R^1 is H, OH, OMe, O-(C_1 - C_{30})-alkyl, O-aryl -(C_1 - C_{30})-alkyl, O-(C_2 - C_{30})-alkenyl, O-(C_3 - C_{30})-cycloalkyl or null and R^2 is H or OH, or R^1 and R^2 form together -O-
- $R^3 = R^4 = \text{OMe}$ or R^3 and R^4 form together -OCH₂O-
- 15 • R is H, C_1 - C_{30} alkyl or O-protecting group and R^6 represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or

heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms, including or not heteroatom(s), or R and R⁶ form together -CMe₂-

- n is 0 to 8.
 - R⁵ is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or O-aryl.
 - the dotted line is null or forms a double bond depending on the meaning of R¹,
 - Z = O or S, and
 - R¹⁷ represents C₁-C₃₀alkyl, C₂-C₃₀alkenyl, C₃-C₃₀cycloalkyl, C₂-C₃₀alkynyl, aryl-(C₁-C₃₀)-alkyl or aryl and advantageously methyl or ethyl,
- can also be used instead of the compounds of formula IV to prepare, according to the process A, the product of formula (I).

Advantageously, the esterification agent in process A is a lewis acid or a protonic acid.

- 15 In an advantageous embodiment of the process A according to the present invention, the amphoteric acid of formula (III) is activated with an imide or by formation of a mixte anhydride or an acid chloride.

Advantageously, the imide is dicyclohexylcarbodiimide or diisopropylcarbodiimide

- 20 More advantageously the mixte anhydride is formed with 2,4,6-trichlorobenzoic acid by contact with 2,4,6-trichlorobenzoyl chloride in the presence of a base.

- In another advantageous embodiment of the process A according to the present invention, the steps i) and ii) are carried out simultaneously, without isolation of the amphoteric acid of formula (III), via a reaction of transesterification performed in presence of an acidic or basic catalyst.

Advantageously, the catalyst is a base, such as an alkaline hydride.

More advantageously, the catalyst is a lewis acid or a protonic acid.

- 30 Given their pharmacological properties, the compounds of the present invention may be used in human therapy in the treatment of cancer pathology.

This invention includes also a pharmaceutical composition which comprises a therapeutically effective amount of at least one compound according to the present invention with one or more pharmaceutically acceptable carriers, excipients or diluents.

5 These pharmaceutical compositions may be formulated for oral, intravenous or subcutaneous administration.

Another aspect of the invention is the use of at least one compound according to the present invention or of the pharmaceutical composition as described above as (i) chemotherapeutic agent, (ii) enhancer of other
10 chemotherapeutic agents (iii) for inhibiting tumors growth, (iv) for inhibiting mammalian parasites, .

Yet, another aspect of the invention is the use of at least one compound according to the present invention for the preparation of a pharmaceutical composition as (i) chemotherapeutic agent, (ii) enhancer of other
15 chemotherapeutic agents (iii) for inhibiting tumors growth, (iv) for inhibiting mammalian parasites, or (v) as reversal agents in particular of harringtonines. (a reversal agent is an agent able to reverse the cell multiresistance phenomenon).

Finally, the present invention describes a method for treating mammalian
20 tumors which comprises administering to a mammal a therapeutically effective amount of at least one compound according to the present invention.

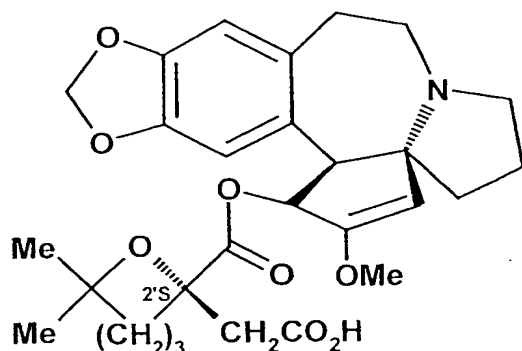
Another advantages of the compounds according to the present invention, is its activity on leukemic cell lines exhibiting resistance to other agents including
25 harringtonines.

The following examples, which are given without implied limitation, illustrates the present invention.

30

Example 1

Preparation of (-)-cephalotaxyl (2'S)-2-carboxymethyl-6,6-dimethyl-2-tetrahydropyranecarboxylate or 4'-demethyl-anhydro-epi-homoharringtonine :



To a stirred solution of anhydro-epi-homoharringtonine (5 g, 9.48 mmol) in ethanol (162.5 ml) was added potassium hydroxide (5.35mg, 94.8 mmol) and water (50 ml). After stirring 7 hours at ambient temperature and evaporation of ethanol under reduced pressure, the residual aqueous layer is saturated with sodium chloride and extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried over magnesium sulfate, and evaporated to dryness.

The resulting crude product was purified by column chromatography (silica 15-40 μ m (50g), dichloromethane then dichloromethane / methanol, 90:10 to 75:25) to provide the expected compound (4.6g, 95%). The product thus obtained showed the following characteristics:

15

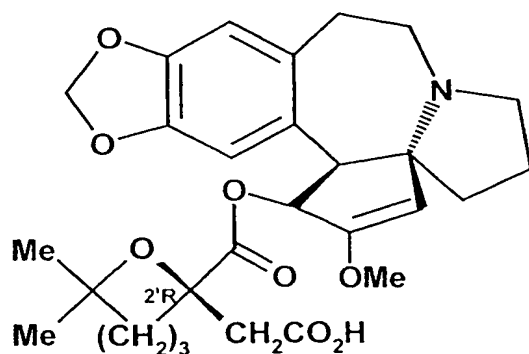
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.61 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.85 (3H, m, H-3 + OCH_2O), 5.06 (1H, s, H-1), 3.80 (1H, d, $J_{4-3} = 9.6$, H-4), 3.68 (3H, s, OCH_3), 3.09 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.37 (1H, dd, $J_{AB} = 14.0$, J = 6.7, H-11 α), 2.16 and 1.90 (2H, 2d, $J_{AB} = 12.3$, CH_2CO_2), 2.02 (1H, m, H-6 α), 1.90 (1H, m, H-6 β), 1.76 (2H, m, CH_2 -7), 1.5 - 1.2 (6H, m, $3 \times \text{CH}_2$), 1.26 (3H, s, CH_3), 1.05 (3H, s, CH_3).

25

Example 2

Preparation of (-)-cephalotaxyl (2'R)-2-carboxymethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-demethyl-anhydro-homoharringtonine :



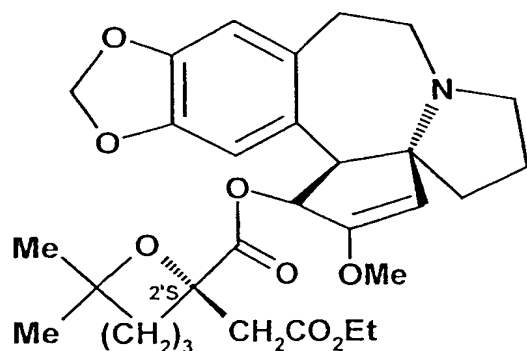
To a stirred solution of anhydro-homoharringtonine (1g, 1.9 mmol) in ethanol (32.5 ml) was added potassium hydroxide (1.07g, 19 mmol) and water (10 ml). After stirring 6 hours at ambient temperature and evaporation of ethanol under reduced pressure, the residual aqueous layer is saturated with sodium chloride and extracted with dichloromethane (3 x 25 ml). The combined organic layers were dried over magnesium sulfate, and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (10g), dichloromethane then dichloromethane / methanol, 98:2 to 80:20) to provide the expected compound (678 mg, 69.5%). The product thus obtained showed the following characteristics:

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.64 (1H, s, H-17), 6.56 (1H, s, H-14), 5.90 (3H, br,s, H-3 + OCH_2O), 5.07 (1H, s, H-1), 3.80 (1H, d, $J_{4,3} = 9.6$, H-4), 3.71 (3H, s, OCH_3), 3.09 (2H, m, H-11 β + H-8 α), 2.95 (1H, dd, $J_{AB} = 11.6$, $J = 6.9$, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.37 (1H, dd, $J_{AB} = 14.0$, $J = 6.7$, H-11 α), 2.07 and 2.02 (2H, 2d, $J_{AB} = 9.6$, CH_2CO_2), 1.91 (1H, m, H-6 α), 1.75 (3H, m, H-6 β + CH_2 -7), 1.6 - 1.0 (6H, m, $\times\text{CH}_2$), 1.22 (3H, s, CH_3), 1.09 (3H, s, CH_3).

Example 3

Preparation of (-)-cephalotaxyl (2'S)-2-ethoxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-ethyl-4'-demethyl-anhydro-epi-homoharringtonine :



1°) Method A

A mixture of 4'-demethyl-anhydro-epi-homoharringtonine resulting from
 5 Example 1 (100 mg, 0.195 mmol) and a solution of boron trifluoride-etherate in
 ethanol 1.5 M (1.12 ml, 0.973 mmol) was stirred at ambient temperature for 15
 hours and at 50°C for 5 hours. After cooling of the reaction mixture, sodium
 hydroxide 2N was added to pH 10 and the resulting layer was extracted with
 10 dichloromethane (3 x 10 ml). The combined organic layers were washed with
 brine (50 ml), dried over magnesium sulfate and evaporated to dryness to provide
 the expected compound (80 mg crude, 76%). The crude product thus obtained
 showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

15 6.62 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.85 (3H, m, H-3 + OCH₂O), 5.02 (1H, s,
 H-1), 4.05 (2H, m, OCH₂CH₃), 3.79 (1H, d, J₄₋₃ = 9.6, H-4), 3.65 (3H, s, OCH₃),
 3.26 (1H, m, H-11β), 3.13 (1H, m, H-8α), 2.99 (1H, m, H-10α), 2.66 (2H, m, H-8β
 + H-10β), 2.43 (1H, dd, J_{AB} = 14.5, J = 6.7, H-11α), 2.12 and 1.78 (2H, 2d, J_{AB} =
 14.2, CH₂CO₂), 2.04 (1H, m, H-6_A), 1.88 (1H, m, H-6_B), 1.78 (2H, m, CH₂-7), 1.5 -
 20 0.9 (6H, m, 3×CH₂), 1.22 (3H, t, J = 7.2, OCH₂CH₃), 1.16 (3H, s, CH₃), 1.02 (3H,
 s, CH₃).

2°) Method B

Sodium hydride 60% (0.5 mg, 0.037 mmol) was added to a solution of
 25 anhydro-epi-homoharringtonine (39 mg, 0.074 mmol) resulting from Example 1 in
 dry ethanol (1 ml) and the resulting mixture was stirred at ambient temperature for
 48 hours. After addition of water (5 ml) the resulting aqueous layer was extracted
 with ether (2 x 5 ml). The combined organic layers were washed with brine (2 x
 100 ml), dried over magnesium sulfate and evaporated to dryness to provide the

expected product (24 mg crude, 60%). The product thus obtained showed identical characteristics to this obtained with method A.

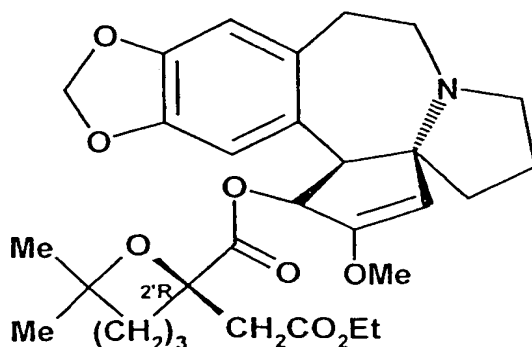
3°) Method C

5 To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (50 mg, 0.097 mmol) resulting from Example 1 in dry dichloromethane (0.35 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (13 μ l, 0.097 mmol) and 2,4,6-trichlorobenzoyl chloride (15 μ l, 0.097 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2 hours a solution of 4-
10 dimethylaminopyridine (23.8 mg, 0.195 mmol) and ethanol (10 μ l, 0.175 mmol) in dry dichloromethane (0.15 ml) was added. After stirring at ambient temperature for 2.5 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting
15 aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product thus obtained (44 mg crude, 85%) showed identical characteristics to this obtained with method A.

20

Example 4

Preparation of (-)-cephalotaxyl (2'R)-2-ethoxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-ethyl-4'-demethyl-anhydro-homoharringtonine :



25

To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (256 mg, 0.498 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (69 μ l, 0.498 mmol) and

2,4,6-trichlorobenzoyl chloride (78 μ l, 0.498 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (121 mg, 0.996 mmol) and ethanol (58 μ l, 0.996 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 5 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (7 ml), with saturated sodium hydrogen carbonate solution (7 ml), with brine (5 ml). After a last extraction of the combined aqueous layers with dichloromethane (10 ml) the combined organic layers were dried over magnesium sulfate and evaporated to 10 dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99:1 to 97:3) to provide the expected compound (241 mg, 89%). The product thus obtained showed the following characteristics:

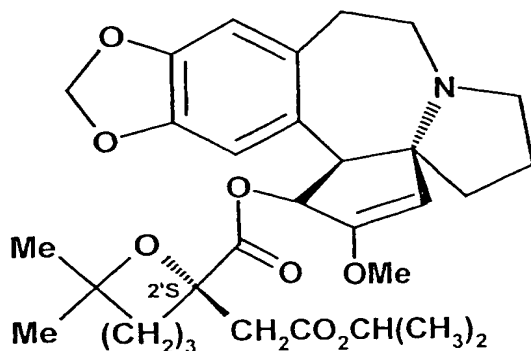
15 IR (film) (cm⁻¹) : 1735 (CO₂), 1657 (C=C-O), 1504 (Ar), 1221 (C-O), 1141 (C-O), 1080 (C-O), 1034 (C-O), 930.

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.92 (1H, d, J_{3,4} = 9.5, H-3), 5.89 and 20 5.81 (2H, 2s, OCH₂O), 5.06 (1H, s, H-1), 4.06 (2H, m, OCH₂CH₃), 3.78 (1H, d, H-4), 3.72 (3H, s, OCH₃), 3.20 (2H, m, H-11 β + H-8 α), 3.01 (1H, m, H-10 α), 2.67 (2H, m, H-8 β + H-10 β), 2.41 (1H, m, H-11 α), 2.14 and 1.66 (2H, 2d, JAB = 14.4, CH₂CO₂), 2.06 (1H, m, H-6_A), 1.80 (1H, m, H-6_B), 1.68 (2H, m, CH₂-7), 1.65 – 1.2 (6H, m, 3 \times CH₂), 1.21 (3H, t, J = 7.1, OCH₂CH₃), 1.10 (3H, s, CH₃), 1.01 (3H, s, 25 CH₃).

Example 5

30 Preparation of (-)-cephalotaxyl (2'S)-2-isopropoxyloxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-isopropyl-4'-demethyl-anhydro-epi-homoharringtonine :



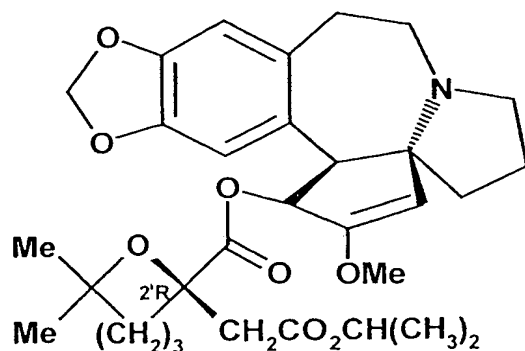
A mixture of 4'-demethyl-anhydro-epi-homoharringtonine resulting from Example 1 (100 mg, 0.195 mmol) and a solution of boron trifluoride-etherate in isopropanol 6 M (1.5 ml, 3.9 mmol) was stirred at ambient temperature for 15 hours. The reaction mixture was alkalinized to pH 10 with sodium hydroxide 2N (6 ml) and the resulting layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with brine (10 ml), dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (2.4g), dichloromethane then dichloromethane / methanol, 99:1) to provide the expected compound (56 mg, 52%). The product thus obtained showed the following characteristics:

$^1\text{H NMR}$ 400 MHz (CDCl_3) (δ ppm, J Hz):

6.61 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.84 (3H, m, H-3 + OCH_2O), 5.02 (1H, s, H-1), 4.92 (1H, m, J = 6.2, $\text{CH}(\text{CH}_3)_2$), 3.78 (1H, d, $J_{4-3} = 9.6$, H-4), 3.65 (3H, s, OCH_3), 3.24 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.40 (1H, dd, JAB = 14.4, J = 6.6, H-11 α), 2.08 and 1.71 (2H, 2d, $J_{AB} = 13.8$, CH_2CO_2), 2.01 (1H, m, H-6 α), 1.9 - 1.0 (6H, m, $3 \times \text{CH}_2$), 1.86 (1H, m, H-6 β), 1.75 (2H, m, CH_2 -7), 1.20 (6H, d, J = 6.2, $\text{CH}(\text{CH}_3)_2$), 1.12 (3H, s, CH_3), 1.01 (3H, s, CH_3).

Example 6

Preparation of (-)-cephalotaxyl (2'R)-2-isopropoxyloxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-isopropyl-4'-demethyl-anhydro-homoharringtonine :



To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (255 mg, 0.498 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (69 μ l, 0.498 mmol) and 2,4,6-trichlorobenzoyl chloride (78 μ l, 0.498 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (121 mg, 0.996 mmol) and isopropanol (76 μ l, 0.996 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (7 ml), with saturated sodium hydrogen carbonate solution (7 ml), with brine (7 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (8), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (216 mg, 78%). The product thus obtained showed the following characteristics:

IR (film) (cm^{-1}): 1731 (CO_2), 1656 ($\text{C}=\text{C}-\text{O}$), 1504 (Ar), 1223 ($\text{C}-\text{O}$), 1142 ($\text{C}-\text{O}$), 1108 ($\text{C}-\text{O}$), 1036 ($\text{C}-\text{O}$), 914.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-14*), 6.59 (1H, s, H-17*), 5.91 (1H, d, $J_{3,4} = 9.6$, H-3), 5.88 and 5.79 (2H, 2s, OCH_2O), 5.04 (1H, s, H-1), 4.93 (1H, m, $J = 6.3$, $\text{CH}(\text{CH}_3)_2$), 3.79 (1H, d, $J_{4,3} = 9.3$, H-4), 3.72 (3H, s, OCH_3), 3.19 (2H, m, H-11 β + H-8 α), 2.99 (1H, m, H-10 α), 2.62 (2H, m, H-8 β + H-10 β), 2.41 (1H, m, H-11 α), 2.09 and 1.70 (2H, 2d, $J_{AB} = 14.1$, CH_2CO_2), 2.04 (1H, m, H-6 Λ), 1.91 (1H, m, H-6 B), 1.77 (2H, m,

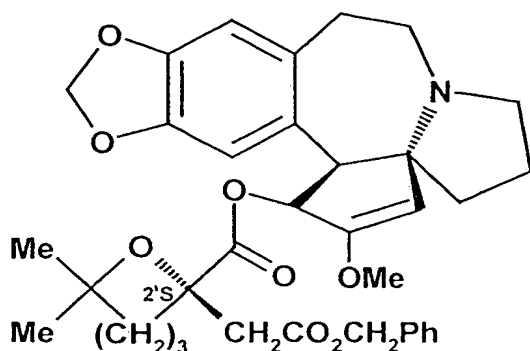
CH₂-7), 1.65 - 1.2 (6H, m, 3×CH₂), 1.19 (6H, d, J = 6.3, CH(CH₃)₂), 1.11 (3H, s, CH₃), 1.02 (3H, s, CH₃).

Example 7

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Preparation of (-)-cephalotaxyl (2'S)-2-benzyloxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-benzyl-4'-demethyl-anhydro-epi-homoharringtonine :

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To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (62 mg, 0.12 mmol) resulting from Example 1 in dry dichloromethane (0.43 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (17 μ l, 0.12 mmol) and 2,4,6-trichlorobenzoyl chloride (19 μ l, 0.12 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (29 mg, 0.14 mmol) and benzylic alcohol (25 μ l, 0.24 mmol) in dry dichloromethane (0.19 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (3g), dichloromethane then dichloromethane / methanol, 99.5:0.5 to 98.5:1.5) to provide the expected compound (40 mg, 55%). The product thus obtained showed the following characteristics:

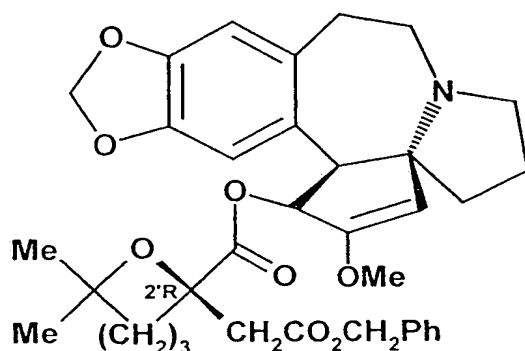
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

7.35 (5H, m, Ph), 6.58 (1H, s, H-17), 6.47 (1H, s, H-14), 5.81 and 5.71 (2H, 2d, $J_{AB} = 1.4$, OCH₂O), 5.81 (1H, d, $J = 9.2$, H-3), 5.08 and 4.99 (2H, 2d, $J_{AB} = 12.4$, OCH₂Ph), 5.0 (1H, s, H-1), 3.70 (1H, d, $J_{4,3} = 9.7$, H-4), 3.63 (3H, s, OCH₃), 3.23 (1H, m, H-11 β), 3.08 (1H, m, H-8 α), 2.93 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.37 (1H, dd, $J_{AB} = 14.3$, $J = 7.0$, H-11 α), 2.16 and 1.80 (2H, 2d, $J_{AB} = 14.3$, CH₂CO₂), 2.0 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.6 - 0.8 (6H, m, 3 \times CH₂), 1.07 (3H, s, CH₃), 1.02 (3H, s, CH₃).

Example 8

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Preparation of (-)-cephalotaxyl (2'R)-2-benzyloxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-benzyl-4'-demethyl-anhydro-homoharringtonine :



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To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (255 mg, 0.496 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (69 μ l, 0.496 mmol) and 2,4,6-trichlorobenzoyl chloride (78 μ l, 0.496 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (121 mg, 0.992 mmol) and benzylic alcohol (102 μ l, 0.992 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (0.8 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography

(silica 15-40 μm (8g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (278 mg, 93%). The product thus obtained showed the following characteristics:

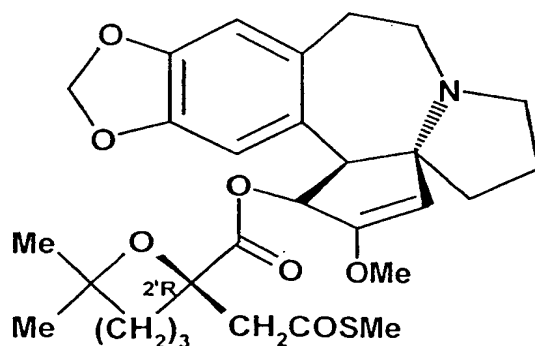
5 IR (film) (cm^{-1}): 1737 (CO_2), 1656 ($\text{C}=\text{C}-\text{O}$), 1504 (Ar), 1222 ($\text{C}-\text{O}$), 1141 ($\text{C}-\text{O}$), 1081 ($\text{C}-\text{O}$), 1036 ($\text{C}-\text{O}$), 911.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

7.34 (5H, m, Ph), 6.60 (1H, s, H-17), 6.52 (1H, s, H-14), 5.91 (1H, d, $J = 9.8$, H-3),
 10 5.77 and 5.61 (2H, 2s, OCH_2O), 5.05 (2H, s, OCH_2Ph), 5.03 (1H, s, H-1), 3.75
 (1H, d, $J_{4,3} = 9.7$, H-4), 3.67 (3H, s, OCH_3), 3.11 (2H, m, H-11 β + H-8 α), 2.93
 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.36 (1H, dd, $J_{AB} = 14.0$, $J = 6.6$, H-
 11 α), 2.18 and 1.66 (2H, 2d, $J_{AB} = 14.5$, CH_2CO_2), 2.0 (1H, m, H-6 α), 1.89 (1H, m,
 H-6 β), 1.75 (2H, m, CH_2-7), 1.7 – 1.2 (6H, m, $3 \times \text{CH}_2$), 1.06 (3H, s, CH_3), 1.04 (3H,
 15 s, CH_3).

Example 9

20 Preparation of (-)-cephalotaxyl (2'R)-2-methylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-methylthio-4'-demethoxy-anhydro-homoharringtonine :



25 To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (404 mg, 0.786 mmol) resulting from Example 2 in dry dichloromethane (2.75 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (105 μl , 0.786 mmol) and 2,4,6-trichlorobenzoyl chloride (123 μl , 0.786 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-

dimethylaminopyridine (192 mg, 1.57 mmol) in dry dichloromethane (0.8 ml) and methanethiol (218 μ l, 1.57 mmol) were added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (10 ml). The resulting organic layer was successively washed with water (14 ml), with saturated sodium hydrogen carbonate solution (14 ml), with brine (14 ml). The resulting aqueous layer was extracted with dichloromethane (20 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (12g), dichloromethane then dichloromethane / methanol, 99:1 to 96:4) to provide the expected compound (228 mg, 53%). The product thus obtained showed the following characteristics:

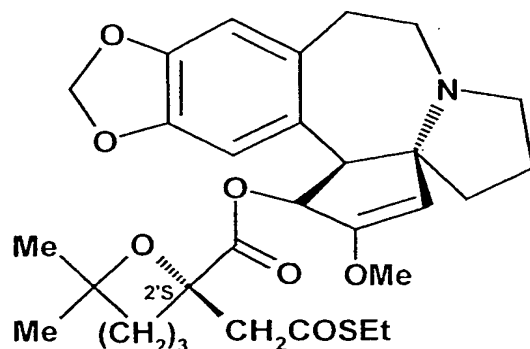
IR (film) (cm^{-1}): 1741 (CO_2), 1690 (COS), 1656 (C=C-O), 1504 (Ar), 1222 (C-O), 1142 (C-O), 1078 (C-O), 1035 (C-O), 913.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.64 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.91 (1H, d, $J_{3-4} = 9.7$, H-3), 5.88 and 5.84 (2H, 2s, OCH_2O), 5.04 (1H, s, H-1), 3.79 (1H, H-4), 3.70 (3H, s, OCH_3), 3.10 (2H, m, H-11 β + H-8 α), 2.95 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.35 (1H, d, $J_{AB} = 14.5$, CH_ACOS) and (1H, m, H-11 α), 2.23 (3H, s, SCH_3), 2.03 (1H, m, H-6 $_A$), 1.90 (1H, m, H-6 $_B$), 1.75 (2H, m, CH_2 -7), 1.8 – 1.2 (7H, m, $3 \times \text{CH}_2$ + CH_BCOS), 1.14 (3H, s, CH_3), 1.03 (3H, s, CH_3).

Example 10

Preparation of (-)-cephalotaxyl (2'S)-2-ethylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-ethylthio-4'-demethoxy-anhydro-epi-homoharringtonine:



To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (70 mg, 0.136 mmol) resulting from Example 1 in dry dichloromethane (0.49 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (19 μ l, 0.136 mmol) and 2,4,6-trichlorobenzoyl chloride (21 μ l, 0.136 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (33 mg, 0.272 mmol) and ethanethiol (20 μ l, 0.272 mmol) in dry dichloromethane (0.25 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (2g), dichloromethane / methanol, 99:1) to provide the expected compound (40 mg, 53%). The product thus obtained showed the following characteristics:

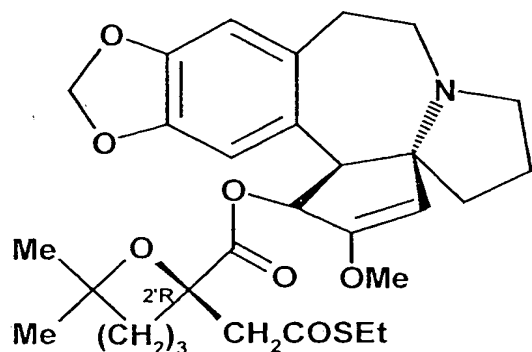
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.64 (1H, s, H-14*), 6.56 (1H, s, H-17*), 5.87 and 5.83 (3H, 2d, J_{AB} = 1.5, OCH₂O + H-3), 5.02 (1H, s, H-1), 3.78 (1H, d, $J_{4,3}$ = 9.7, H-4), 3.65 (3H, s, OCH₃), 3.24 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.95 (1H, m, H-10 α), 2.79 (2H, m, SCH₂CH₃), 2.60 (2H, m, H-8 β + H-10 β), 2.41 (1H, dd, J_{AB} = 14.2, J = 7.0, H-11 α), 2.28 and 1.83 (2H, 2d, J_{AB} = 14.4, CH₂COS), 2.01 (1H, m, H-6_A), 1.91 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.5 - 0.85 (6H, m, 3 \times CH₂), 1.20 (3H, t, J = 7.4, SCH₂CH₃), 1.14 (3H, s, CH₃), 1.01 (3H, s, CH₃).

Example 11

Preparation of (-)-cephalotaxyl (2'R)-2-ethylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-ethylthio-4'-demethoxy-anhydro-homoharringtonine :

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To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (250 mg, 0.486 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (68 μ l, 0.486 mmol) and 2,4,6-trichlorobenzoyl chloride (76 μ l, 0.486 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (119 mg, 0.973 mmol) and ethanethiol (72 μ l, 0.973 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (7 ml), with saturated sodium hydrogen carbonate solution (7 ml), with brine (7 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (7g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (251 mg, 93%). The product thus obtained showed the following characteristics:

IR (film) (cm^{-1}) : 1740 (CO_2), 1688 (COS), 1657 (C=C-O), 1504 (Ar), 1223 (C-O), 1142 (C-O), 1078 (C-O), 1037 (C-O), 910.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.64 (1H, s, H-14*), 6.59 (1H, s, H-17*), 5.91 (1H, H-3), 5.90 and 5.85 (2H, 2s, OCH_2O), 5.03 (1H, s, H-1), 3.80 (1H, H-4), 3.71 (3H, s, OCH_3), 3.14 (2H, m, H-

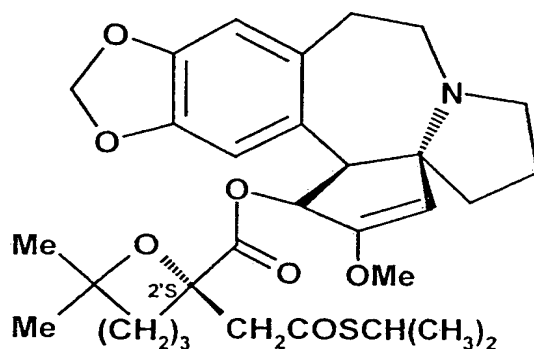
11 β + H-8 α), 2.88 (1H, m, H-10 α), 2.81 (2H, m, SCH₂CH₃), 2.61 (2H, m, H-8i) + H-10 β), 2.38 (1H, m, H-11D), 2.35 (1H, d, JAB = 14.8, CH_ACOS), 2.02 (1H, m, H-6_A), 1.91 (1H, m, H-6_B), 1.77 (2H, m, CH₂-7), 1.65 – 1.1 (7H, m, 3 \times CH₂ + CH_BCOS), 1.20 (3H, t, J = 7.4, SCH₂CH₃), 1.14 (3H, s, CH₃), 1.02 (3H, s, CH₃).

5

Example 12

Preparation of (-)-cephalotaxyl (2'S)-2-isopropylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyran carboxylate or 4'-isopropylthio-4'-demethoxy-anhydro-epi-homoharringtonine :

10



To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (49 mg, 0.095 mmol) resulting from Example 1 in dry dichloromethane (0.34 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (13 μ l, 0.095 mmol) and 2,4,6-trichlorobenzoyl chloride (15 μ l, 0.095 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (23 mg, 0.19 mmol) and isopropanethiol (18 μ l, 0.19 mmol) in dry dichloromethane (0.2 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (1g), dichloromethane / methanol, 99:1) to provide the expected compound (40 mg, 74%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz) :

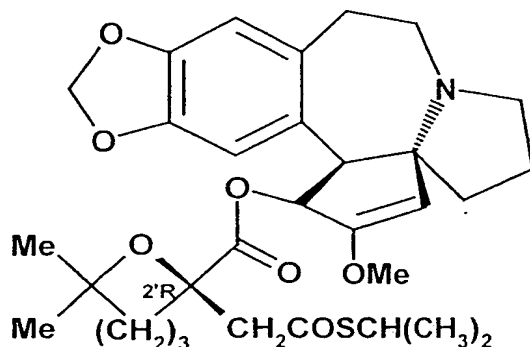
6.64 (1H, s, H-14*), 6.57 (1H, s, H-17*), 5.87 (3H, 2d, J_{AB} = 1.4, OCH₂O + H-3), 5.02 (1H, s, H-1), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.65 (3H, s, OCH₃), 3.55 (1H, m, J = 6.9, CH(CH₃)₂), 3.23 (1H, m, H-11β), 3.09 (1H, m, H-8α), 2.94 (1H, m, H-10α), 2.60 (2H, m, H-8β + H-10β), 2.42 (1H, dd, J_{AB} = 13.9, J = 6.8, H-11α), 2.25 and 1.79 (2H, 2d, J_{AB} = 14.3, CH₂COS), 2.04 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.45 - 0.85 (6H, m, 3×CH₂), 1.25 (6H, d, J = 6.9, CH(CH₃)₂), 1.14 (3H, s, CH₃), 1.01 (3H, s, CH₃).

10

Example 13

Preparation of (-)-cephalotaxyl (2'R)-2-isopropylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-isopropylthio-4'-demethoxy-anhydro-homoharringtonine :

15



To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (248 mg, 0.483 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (67 μl, 0.483 mmol) and 2,4,6-trichlorobenzoyl chloride (76 μl, 0.483 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (120 mg, 0.965 mmol) and isopropanethiol (90 μl, 0.965 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (7 ml), with saturated sodium hydrogen carbonate solution (7 ml), with brine (7 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography

(silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (267 mg, 97%). The product thus obtained showed the following characteristics:

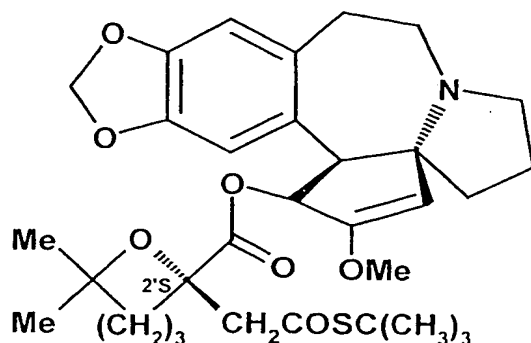
- 5 IR (film) (cm^{-1}): 1740 (CO_2), 1687 (COS), 1656 ($\text{C}=\text{C}-\text{O}$), 1504 (Ar), 1223 ($\text{C}-\text{O}$), 1142 ($\text{C}-\text{O}$), 1078 ($\text{C}-\text{O}$), 1036 ($\text{C}-\text{O}$), 912.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

- 6.64 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.91 (1H, d, $J_{3,4} = 9.7$, H-3), 5.89
 10 and 5.85 (2H, 2s, OCH_2O), 5.04 (1H, s, H-1), 3.79 (1H, d, H-4), 3.71 (3H, s, OCH_3), 3.56 (1H, m, $J = 6.9$, $\text{CH}(\text{CH}_3)_2$), 3.18 (2H, m, H-11 β + H-8 α), 2.99 (1H, m, H-10 α), 2.61 (2H, m, H-8 β + H-10 β), 2.39 (1H, m, H-11 α), 2.31 (1H, d, $J_{AB} = 14.3$, CH_ACOS), 2.04 (1H, m, H-6 $_A$), 1.92 (1H, m, H-6 $_B$), 1.78 (2H, m, CH_2 -7), 1.7 – 1.2 (7H, m, $3 \times \text{CH}_2$ + CH_BCOS), 1.25 and 1.24 (6H, 2d, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$),
 15 1.13 (3H, s, CH_3), 1.0 (3H, s, CH_3).

Example 14

- Preparation of (-)-cephalotaxyl (2'S)-2-tert-butylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-tert-butylthio-4'-demethoxy-anhydro-epi-homoharringtonine :



- 25 To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (70 mg, 0.136 mmol) resulting from Example 1 in dry dichloromethane (0.49 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (19 μ l, 0.136 mmol) and 2,4,6-trichlorobenzoyl chloride (21 μ l, 0.136 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (33 mg, 0.272 mmol) and tert-butanethiol (31 μ l, 0.272
 30

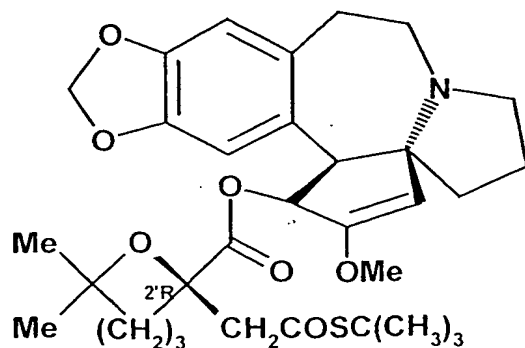
mmol) in dry dichloromethane (0.3 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The
5 resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (1.5g), dichloromethane / methanol, 99:1) to provide the expected compound (46 mg, 58%). The product thus obtained showed the
10 following characteristics:

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.65 (1H, s, H-14*), 6.56 (1H, s, H-17*), 5.87 and 5.84 (2H, -2d, $J_{AB} = 1.5$, OCH_2O), 5.84 (1H, d, $J_{3,4} = 10.0$, H-3), 5.02 (1H, s, H-1), 3.78 (1H, d, $J_{4,3} = 9.6$, H-4), 3.64 (3H, s, OCH_3), 3.24 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.96 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.42 (1H, dd, $J_{AB} = 14.3$, $J = 7.0$, H-11 α), 2.20 and 1.71 (2H, 2d, $J_{AB} = 14.1$, CH_2COS), 2.01 (1H, m, H-6 α), 1.88 (1H, m, H-6 β), 1.75 (2H, m, CH_2 -7), 1.6 - 0.85 (6H, m, $3 \times \text{CH}_2$), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.13 (3H, s, CH_3), 1.01 (3H, s, CH_3).
20

Example 15

Preparation of (-)-cephalotaxyl (2'R)-2-tert-butylthiocarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-tert-butylthio-4'-demethoxy-anhydro-homoharringtonine :
25



To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (234 mg, 0.455 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added
30

at 0°C triethylamine (dried over potassium hydroxide) (63 μ l, 0.455 mmol) and 2,4,6-trichlorobenzoyl chloride (72 μ l, 0.455 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (111 mg, 0.911 mmol) and *tert*-butanethiol (102 μ l, 0.911 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (7 ml), with saturated sodium hydrogen carbonate solution (7 ml), with brine (7 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (6g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (212 mg, 81%). The product thus obtained showed the following characteristics:

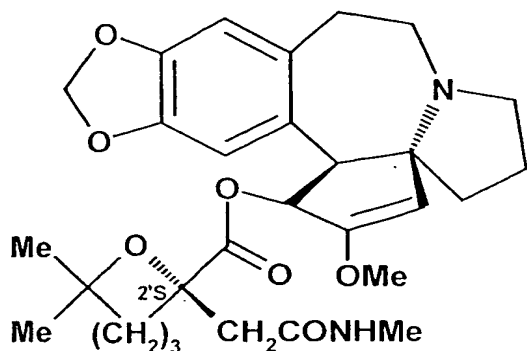
IR (film) (cm^{-1}): 1738 (CO_2), 1681 (COS), 1659 (C=C-O), 1504 (Ar), 1222 (C-O), 1141 (C-O), 1077 (C-O), 1037 (C-O), 911.

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.65 (1H, s, H-14*), 6.59 (1H, s, H-17*), 5.89 (3H, m, OCH_2O + H-3), 5.03 (1H, s, H-1), 3.76 (1H, H-4), 3.72 (3H, s, OCH_3), 3.13 (2H, m, H-11 β + H-8 α), 3.0 (1H, m, H-10 α), 2.63 (2H, m, H-8 β + H-10 β), 2.40 (1H, m, H-11 α), 2.23 (1H, d, $J_{AB} = 12.2$, CH_ACOS), 2.01 (1H, m, H-6A), 1.93 (1H, m, H-6B), 1.78 (2H, m, CH_2 -7), 1.7 – 1.2 (6H, m, $3\times\text{CH}_2$ + CH_BCOS), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.12 (3H, s, CH_3), 0.99 (3H, s, CH_3).

Example 16

Preparation of (-)-cephalotaxyl (2'S)-2-(methylamino)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-methylamino-4'-demethoxy-anhydro-epi-homoharringtonine :



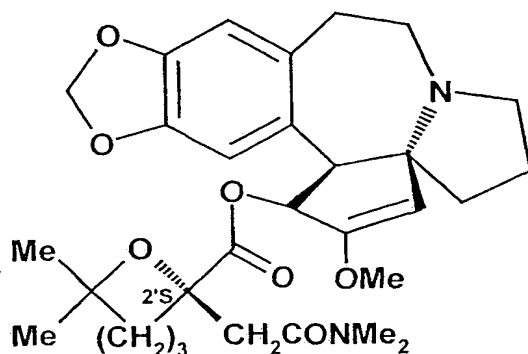
To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (52 mg, 0.10 mmol) resulting from Example 1 in dry dichloromethane (0.34 ml) was added
 5 at 0°C triethylamine (dried over potassium hydroxide) (14 µl, 0.10 mmol) and 2,4,6-trichlorobenzoyl chloride (15.5 µl, 0.10 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (49 mg, 0.40 mmol) in dry dichloromethane (0.3 ml) and methylamine hydrochloride (13.5 mg, 0.20 mmol) were added. After stirring at
 10 ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to
 15 dryness. The resulting crude product was purified by column chromatography (silica 15-40 µm (2g), dichloromethane then dichloromethane / methanol, 98:2) to provide the expected compound (47 mg, 89 %). The product thus obtained showed the following characteristics:

20 ¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):
 6.61 (1H, s, H-14*), 6.59 (1H, s, H-17*), 6.48 (1H, m, NH), 5.85 (3H, m, OCH₂O + H-3), 5.03 (1H, s, H-1), 3.79 (1H, d, J_{4,3} = 9.7, H-4), 3.67 (3H, s, OCH₃), 3.17 (1H, m, H-11β), 3.09 (1H, m, H-8α), 2.93 (1H, m, H-10α), 2.74 (3H, d, J = 4.9, NHCH₃), 2.59 (2H, m, H-8β + H-10β), 2.37 (1H, dd, J_{AB} = 14.2, J = 7.0, H-11α),
 25 2.11 and 1.84 (2H, 2d, J_{AB} = 14.5, CH₂CON), 2.02 (1H, m, H-6A), 1.89 (2H, m, H-6B + CH), 1.75 (2H, m, CH₂-7), 1.4 – 1.1 (5H, m, CH + 2×CH₂), 1.18 (3H, s, CH₃), 0.96 (3H, s, CH₃).

Example 17

Preparation of (-)-cephalotaxyl (2'S)-2-(dimethylamino)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-dimethylamino-4'-demethoxy-anhydro-epi-homoharringtonine :

5



To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (60 mg, 0.117 mmol) resulting from Example 1 in dry dichloromethane (0.4 ml) was added
 10 at 0°C triethylamine (dried over potassium hydroxide) (16.2 μ l, 0.111 mmol) and 2,4,6-trichlorobenzoyl chloride (18 μ l, 0.117 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (28.6 mg, 0.234 mmol) in dry dichloromethane (0.16 ml) and dimethylamine (in excess) were added. After stirring at ambient temperature
 15 for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness.
 20 The resulting crude product was purified by column chromatography (silica 15-40 μ m (1.5g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (11 mg, 17.4 %). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

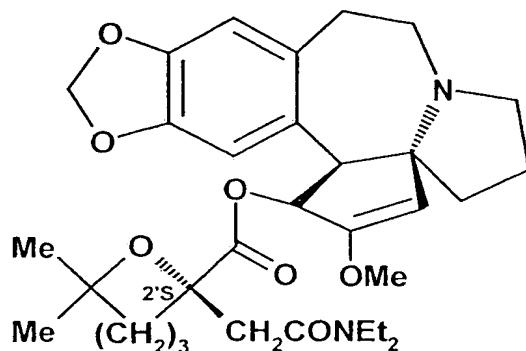
25 6.59 (2H, s, H-17 + H-14), 5.88 (1H, d, J₃₋₄ = 9.7, H-3), 5.84 (2H, s, OCH₂O), 5.01 (1H, s, H-1), 3.80 (1H, d, J₄₋₃ = 9.9, H-4), 3.66 (3H, s, OCH₃), 3.23 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.95 (1H, m, H-10 α) and (3H, s, NCH₃), 2.88 (3H, s, NCH₃), 2.60 (2H, m, H-8' + H-10 β), 2.37 (1H, m, H-11 α), 2.35 and 1.73 (2H, 2d,

$J_{AB} = 13.5$, $\underline{\text{CH}_2\text{CON}}$), 2.01 (2H, m, CH_2-6), 1.95 – 1.10 (8H, m, $\text{CH}_2-7 + 3 \times \text{CH}_2$), 1.08 (3H, s, CH_3), 0.96 (3H, s, CH_3).

Example 18

5

Preparation of (-)-cephalotaxyl (2'S)-2-(diethylamino)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-diethylamino-4'-demethoxy-anhydro-epi-homoharringtonine :



10

To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (57 mg, 0.11 mmol) resulting from Example 1 in dry dichloromethane (0.34 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (15.3 μl , 0.11 mmol) and 2,4,6-trichlorobenzoyl chloride (17.1 μl , 0.11 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (27.4 mg, 0.22 mmol) and diethylamine (23 μl , 0.22 mmol) in dry dichloromethane (0.16 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μm (1.5g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (50 mg, 80%). The product thus obtained showed the following characteristics:

25

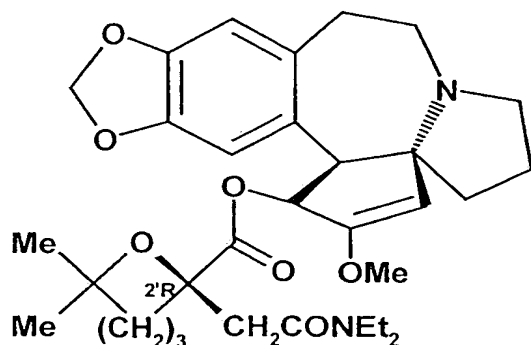
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.60 (1H, s, H-14*), 6.58 (1H, s, H-17*), 5.84 (3H, m, OCH₂O + H-3), 5.02 (1H, s, H-1), 3.81 (1H, d, J_{4,3} = 9.6, H-4), 3.69 (2H, m, NCH₂CH₃), 3.66 (3H, s, OCH₃), 3.21 (1H, m, H-11β), 3.08 (1H, m, H-8α), 2.95 (3H, m, H-10α + NCH₂CH₃), 2.60 (2H, m, H-8β + H-10β), 2.41 and 1.71 (2H, 2d, J_{AB} = 13.3, CH₂CON), 2.37 (1H, dd, J_{AB} = 14.2, J = 7.0, H-11α), 2.01 (1H, m, H-6_A), 2.0 – 1.0 (6H, m, 3×CH₂), 1.89 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.10 (9H, m, N(CH₂CH₃)₂ + CH₃), 0.92 (3H, s, CH₃).

Example 19

10

Preparation of (-)-cephalotaxyl (2'R)-2-(diethylamino)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-diethylamino-4'-demethoxy-anhydro-homoharringtonine :



15

To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (250 mg, 0.487 mmol) resulting from Example 2 in dry dichloromethane (1.8 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (65 μl, 0.487 mmol) and 2,4,6-trichlorobenzoyl chloride (76 μl, 0.487 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (119 mg, 0.974 mmol) and diethylamine (105 μl, 0.974 mmol) in dry dichloromethane (0.8 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography

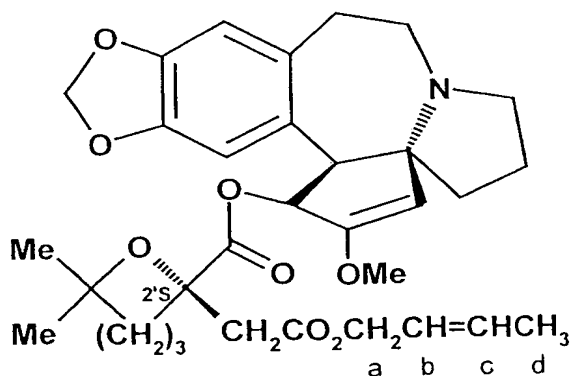
(silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99:1 to 97:3) to provide the expected compound (226 mg, 82%). The product thus obtained showed the following characteristics:

- 5 ^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):
 6.63 (1H, s, H-14*), 6.59 (1H, s, H-17*), 5.86 (1H, d, $J_{3,4} = 9.6$, H-3), 5.82 and
 5.78 (2H, 2s, OCH_2O), 5.04 (1H, s, H-1), 3.81 and 3.72 (2H, 2m, NCH_2CH_3), 3.80
 (1H, d, H-4), 3.70 (3H, s, OCH_3), 3.12 (2H, m, H-11 β + H-8 α), 2.90 (3H, m, H-
 10 α + NCH_2CH_3), 2.59 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J_{AB} = 14.2$, $J = 6.7$,
 10 H-11 α), 2.24 (1H, d, $J_{AB} = 13.1$, CH_ACON), 2.02 (1H, m, H-6 $_A$), 1.95 – 1.15 (10H,
 m, H-6 $_B$ + CH_2 -7 + CH_BCON + $3 \times \text{CH}_2$), 1.06 and 1.03 (6H, 2t, $J = 7.1$,
 $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.04 (3H, s, CH_3), 0.92 (3H, s, CH_3).

Example 20

15

Preparation of (-)-cephalotaxyl (2'S)-2-(but-2-enyl)oxycarbonylmethyl-6,6-
dimethyl-2-tetrahydropyrane carboxylate or 4'-(but-2-enyl)-4'-demethyl-anhydro-
epi-homoharringtonine :



20

1°) Method A

25

To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (60 mg, 0.12 mmol) resulting from Example 1 in dry dichloromethane (0.35 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (17 μ l, 0.12 mmol) and 2,4,6-trichlorobenzoyl chloride (19 μ l, 0.12 mmol) over a period of 10 minutes.

After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (29 mg, 0.14 mmol) and crotyl alcohol (17 μ l, 0.24 mmol) in dry dichloromethane (0.19 ml) was added. After stirring at ambient temperature for 72 hours, the reaction mixture was diluted with dichloromethane (5 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (1g), dichloromethane then dichloromethane / methanol, 99:1 to 97:3) to provide the expected compound (36 mg, 55%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

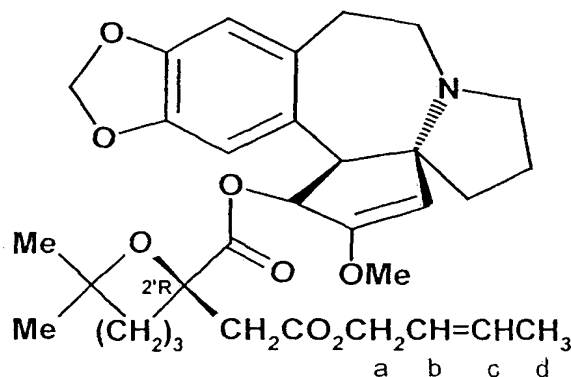
6.61 (1H, s, H-17*), 6.57 (1H, s, H-14*), 5.85 and 5.81 (2H, 2d, J_{AB} = 1.4, OCH₂O), 5.83 (1H, d, J₃₋₂ = 9.6, H-3), 5.75 (1H, dq, J_{c-b'} = 15.2, J_{c-d'} = 6.5, H-c), 5.55 (1H, m, J_{b-c} = 15.3, H-b), 5.02 (1H, s, H-1), 4.46 and 4.38 (2H, 2dd, J_{AB} = 12.3, J_{a-b'} = 6.5, CH₂-a), 3.77 (1H, d, J₄₋₃ = 9.7, H-4), 3.65 (3H, s, OCH₃), 3.23 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.95 (1H, m, H-10 α), 2.61 (2H, m, H-8 β + H-10 β), 2.40 (1H, dd, J_{AB} = 14.2, J = 6.6, H-11 α), 2.13 and 1.78 (2H, 2d, J_{AB} = 14.3, CH₂CO₂), 2.01 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.71 (3H, dd, J_{d-c} = 6.5, J_{d-b} = 1.1, CH₃-d), 1.55 – 1.2 (6H, m, 3 \times CH₂), 1.11 (3H, s, CH₃), 1.01 (3H, s, CH₃).

2°) Method B

Sodium hydride 60% (10 mg, 0.228 mmol) was added to a solution of anhydro-epi-homoharringtonine (100 mg, 0.18 mmol) resulting from Example 1 in crotyl alcohol (1 ml) and the resulting mixture was stirred at ambient temperature for 72 hours. After neutralization by addition of hydrochloric acid 1N, dilution with water (5 ml) and saturation with sodium chloride, the resulting aqueous layer was extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (2g), dichloromethane then dichloromethane / methanol, 99:1) to provide the expected product (66 mg, 62%). The product thus obtained showed identical characteristics to this obtained with method A.

Example 21

Preparation of (-)-cephalotaxyl (2'R)-2-(but-2-enyl)oxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-(but-2-enyl)-4'-demethyl-anhydro-homoharringtonine :



Sodium hydride 60 % (21.9 mg, 0.9 mmol) was added to a solution of anhydro-homoharringtonine (400 mg, 0.767 mmol) in 3-methyl-2-butenol (4 ml) and the resulting mixture was stirred at ambient temperature for 36 hours under argon. After dilution with water (50 ml) the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic layers were diluted with dichloromethane (150 ml), washed with water (50 ml), dried over magnesium sulfate and evaporated to dryness (350 mg crude, 81%). The crude product thus obtained was purified by column chromatography (silica 15-40 μ m (5g), dichloromethane then dichloromethane / methanol, 95:5) to provide the expected product (105 mg, 24.5%). The product thus obtained showed the following characteristics:

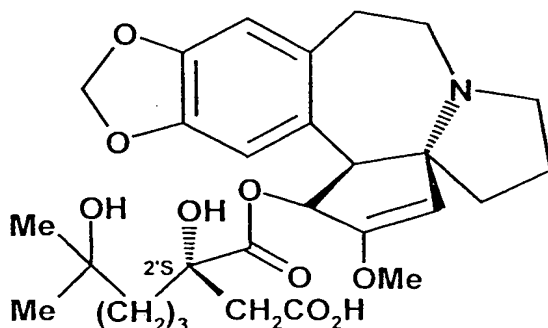
20

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.61 (1H, s, H-17*), 6.57 (1H, s, H-14*), 5.91 (1H, d, $J_{3,2} = 9.4$, H-3), 5.86 and 5.78 (2H, 2d, JAB = 1.4, OCH_2O), 5.72 (1H, m, H-c), 5.55 (1H, m, H-b), 5.03 (1H, s, H-1), 4.43 (2H, m, CH_2 -a), 3.78 (1H, d, $J_{4,3} = 9.7$, H-4), 3.69 (3H, s, OCH_3), 3.11 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.36 (1H, dd, $J_{AB} = 14.1$, $J = 6.9$, H-11 α), 2.13 and 1.60 (2H, 2d, $J_{AB} = 14.43$, CH_2CO_2), 2.0 (1H, m, H-6 $_A$), 1.89 (1H, m, H-6 $_B$), 1.75 (2H, m, CH_2 -7), 1.71 (3H, dd, $J_{d,c} = 5.5$, $J_{d,b} = 1.1$, CH_3 -d), 1.7 – 1.2 (6H, m, $3 \times \text{CH}_2$), 1.10 (3H, s, CH_3), 1.04 (3H, s, CH_3).

Example 22

Preparation of 4'-demethyl-epi-homoharringtonine from epi-homoharringtonine :



5

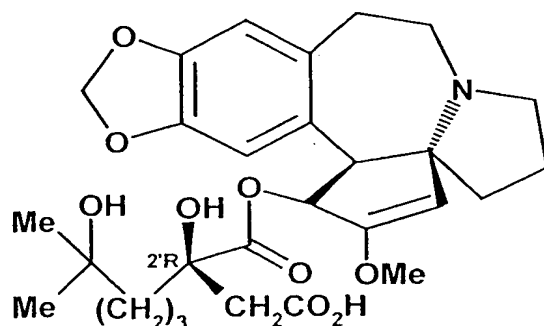
To a stirred solution of epi-homoharringtonine (266 mg, 0.488 mmol) in methanol (6.7 ml) was added lithium hydroxide (119 mg, 0.488 mmol) and water (2.2 ml). After stirring 5 hours at ambient temperature 1N hydrochloric acid was added to pH 7 and ethanol was evaporated under reduced pressure. After addition of dichloromethane (10 ml), the residual aqueous layer is exhausted by trituration with magnesium sulfate. The solid removed by filtration was washed with dichloromethane (4 x 2 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (128 mg crude, 49%). The crude product thus obtained showed the following characteristics:

¹H NMR 400 MHz (DMSO-d₆) (δ ppm, J Hz) :
 6.64 (1H, s, H-17*), 6.57 (1H, s, H-14*), 5.90 (2H, s, OCH₂O), 5.75 (1H, d, J₃₋₄ = 9.5, H-3), 5.11 (1H, s, H-1), 3.95 (1H, s, 2'-OH), 3.78 (1H, d, J₄₋₃ = 9.7, H-4), 3.58 (3H, s, OCH₃), 3.06 (1H, m, H-11β), 2.81 (1H, m, H-8α), 2.68 (1H, m, H-10α), 2.52 (2H, m, H-8β + H-10β), 2.33 (1H, dd, J_{AB} = 13.4, J = 6.3, H-11α), 2.0 (2H, m, CH₂CO₂), 1.9 – 0.6 (10H, m, CH₂-6 + CH₂-7 + 3xCH₂), 0.99 (3H, s, CH₃), 0.97 (3H, s, CH₃).

25

Example 23

Preparation of 4'-demethyl-homoharringtonine from homoharringtonine :



To a stirred solution of homoharringtonine (60 mg, 0.11 mmol) in methanol (1.5 ml) was added lithium hydroxide (27 mg, 1.1 mmol) and water (0.5 ml). After stirring 15 hours at ambient temperature 1N hydrochloric acid was added to pH 7-8 and ethanol was evaporated under reduced pressure. After addition of dichloromethane (5 ml), the residual aqueous layer is exhausted by trituration with magnesium sulfate. The solid removed by filtration was washed with dichloromethane (4 × 2 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (28 mg crude, 48%). The crude product thus obtained showed the following characteristics:

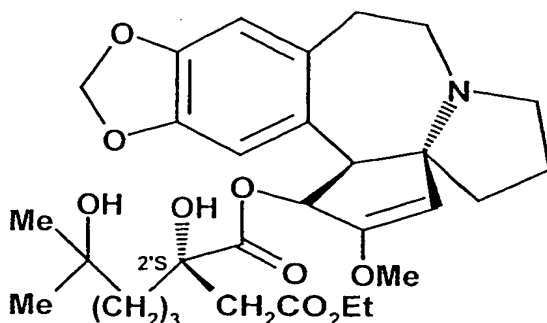
IR (film) (cm^{-1}): 3600-2800 (CO_2H , OH), 1738 (CO_2), 1657 ($\text{C}=\text{C}-\text{O}$), 1505 (Ar), 1223 (C-O), 1166 (C-O), 1080 (C-O), 1041 (C-O), 912.

^1H NMR 400 MHz ($\text{DMSO}-d_6$) (δ ppm, J Hz): 6.63 (1H, s, H-17*), 6.54 (1H, s, H-14*), 5.89 + 5.86 (2H, 2s, OCH_2O), 5.70 (1H, d, $J_{3,4} = 9.6$, H-3), 5.13 (1H, s, H-1), 4.02 (1H, s, 2'-OH), 3.77 (1H, d, $J_{4,3} = 9.6$, H-4), 3.59 (3H, s, OCH_3), 3.04 (1H, m, H-11 β), 2.81 (1H, td, $J = 8.7$ and 3.6), H-8 α), 2.69 (1H, m, H-10 α), 2.52 (2H, m, H-8 β + H-10 β), 2.33 (1H, dd, $J_{AB} = 14.0$, $J = 7.0$, H-11 α), 1.86 (1H, m, H-6 $_A$), 1.81 (1H, m, H-6 $_B$), 1.68 + 1.57 (4H, 2m, CH_2-7 + CH_2CO_2), 1.16 (6H, m, $3 \times \text{CH}_2$), 1.02 (3H, s, CH_3), 1.01 (3H, s, CH_3).

25

Example 24

Preparation of (2'S)-4'-ethyl-4'-demethyl-epi-homoharringtonine:



1°) Method A

To a stirred solution of 4'-ethyl-4'-demethyl-anhydro-epi-homoharringtonine (59 mg, 0.109 mmol) resulting from Example 3 in dry dichloromethane (0.3 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.195 ml, 0.98 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (2.8 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 6 ml) up to pH 8. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 10 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (46 mg crude, 76%). The crude product thus obtained showed the following characteristics:

15

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.64 (1H, s, H-17*), 6.59 (1H, s, H-14*), 5.95 and 5.85 (2H, 2d, J_{AB} = 1.3, OCH₂O), 5.94 (1H, d, J_{3,4} = 9.3, H-3), 5.03 (1H, s, H-1), 4.11 (2H, m, OCH₂CH₃), 3.78 (1H, d, J_{4,3} = 9.8, H-4), 3.65 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.09 (2H, m, H-11β + H-8α), 2.93 (1H, m, H-10α), 2.59 and 2.51 (2H, 2d, J_{AB} = 16.6, CH₂CO₂), 2.57 (2H, m, H-8β + H-10β), 2.38 (1H, dd, J_{AB} = 14.2, J = 6.8, H-11α), 2.02 (1H, m, H-6_A), 1.89 (1H, m, H-6_B), 1.71 (2H, m, CH₂-7), 1.5 - 0.6 (6H, m, 3×CH₂), 1.24 (3H, t, J = 7.2, OCH₂CH₃), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃).

25 2°) Method B

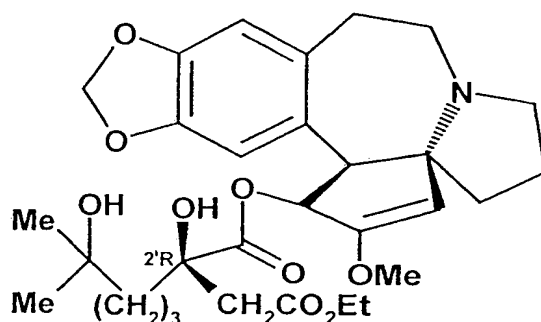
To a stirred mixture of 4'-demethyl-epi-homoharringtonine (40 mg, 0.075 mmol) resulting from Example 22 in dry dichloromethane (0.26 ml) was added at 0°C triethylamine (dried over potassium hydroxide) (10 μl, 0.075 mmol) and 2,4,6-trichlorobenzoyl chloride (12 μl, 0.075 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-

30

dimethylaminopyridine (18.4 mg, 0.15 mmol) and ethanol (8 μ l, 0.138 mmol) in dry dichloromethane (0.16 ml) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was diluted with dichloromethane (10 ml). The resulting organic layer was successively washed with water (5 ml), with saturated sodium hydrogen carbonate solution (5 ml), with brine (5 ml). The resulting aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers after drying over magnesium sulfate were evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (1g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the expected compound (11 mg, 26 %). The product thus obtained showed identical characteristics to this obtained with method A.

Example 25

15 Preparation of (2'R)-4'-ethyl-4'-demethyl-homoharringtonine :



1°) Method A

To a stirred solution of 4'-ethyl-4'-demethyl-anhydro-homoharringtonine (220 mg, 0.406 mmol) resulting from Example 4 in dry dichloromethane (1.1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.728 ml, 3.6 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (10 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 31.5 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99:1 to 98:2) to provide the

expected compound (125 mg, 55%). The product thus obtained showed the following characteristics:

HRMS calcd for $C_{30}H_{42}NO_9$ $[M + H]^+$ 560.2860, obsd 560.2863

5 IR (film) (cm^{-1}): 3516 (OH), 3427 (OH), 1741 (CO_2), 1656 (C=C-O), 1504 (Ar), 1224 (C-O), 1183 (C-O), 1114 (C-O), 1083 (C-O), 1035 (C-O), 911.

1H NMR 400 MHz ($CDCl_3$) (δ ppm, J Hz):

6.62 (1H, s, H-17*), 6.55 (1H, s, H-14*), 5.98 (1H, d, $J_{3,4} = 9.7$, H-3), 5.86 (2H, m, OCH₂O), 5.05 (1H, s, H-1), 4.02 (2H, m, OCH₂CH₃), 3.78 (1H, d, $J_{4,3} = 9.7$, H-4), 3.68 (3H, s, OCH₃), 3.53 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.96 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, m, H-11 α), 2.24 and 1.90 (2H, 2d, $J_{AB} = 16.2$, CH₂CO₂), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.5 - 1.15 (6H, m, 3 \times CH₂), 1.21 (3H, t, J = 7.2, OCH₂CH₃), 1.19 (6H, 2s, 2 \times CH₃).

15

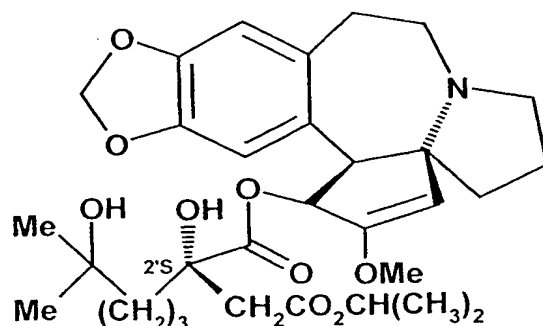
2°) Method B

Sodium hydride 60% (2.4 mg, 0.1 mmol) was added to a solution of homoharringtonine (300 mg, 0.55 mmol) in dry ethanol (30 ml) and the resulting mixture was stirred at ambient temperature for 27 hours. After addition of water (10 ml) the resulting aqueous layer was saturated with sodium chloride and extracted with dichloromethane (3 \times 20 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (65 g), buffer NH₄Cl-HCl / methanol, 82:18). After removal of methanol in vacuo the resulting aqueous layer was alkalized to pH 8-9 and extracted with dichloromethane (3 \times 50 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (298 mg; 97%). The product thus obtained showed identical characteristics to this obtained with method A.

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Example 26

Preparation of (2'S)-4'-isopropyl-4'-demethyl-epi-homoharringtonine :



To a stirred solution of 4'-isopropyl-4'-demethyl-anhydro-epi-homoharringtonine (46 mg, 0.083 mmol) resulting from Example 5 in dry dichloromethane (0.23 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.148 ml, 0.745 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (2.2 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 4 ml) up to pH 8. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 5 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (30 mg crude, 64%). The crude product thus obtained showed the following characteristics:

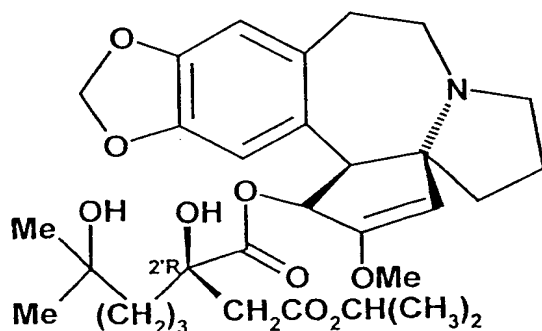
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.64 (1H, s, H-17*), 6.59 (1H, s, H-14*), 5.94 and 5.85 (2H, 2d, J_{AB} = 1.3, OCH₂O), 5.93 (1H, d, J_{3,4} = 9.8, H-3), 5.03 (1H, s, H-1), 4.98 (1H, m, J = 6.2, OCH(CH₃)₂), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.65 (3H, s, OCH₃), 3.54 (1H, s, 2'-OH), 3.09 (2H, m, H-11β + H-8α), 2.94 (1H, m, H-10α), 2.57 and 2.49 (2H, 2d, J_{AB} = 16.6, CH₂CO₂), 2.56 (2H, m, H-8β + H-10β), 2.38 (1H, dd, J_{AB} = 14.0, J = 7.0, H-11α), 2.02 (1H, m, H-6_A), 1.89 (1H, m, H-6_B), 1.71 (2H, m, CH₂-7), 1.5 - 0.6 (6H, m, 3×CH₂), 1.22 and 1.21 (6H, 2d, J = 6.2, OCH(CH₃)₂), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃).

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Example 27

Preparation of (2'R)-4'-isopropyl-4'-demethyl-homoharringtonine :



1°) Method A

- 5 To a stirred solution of 4'-isopropyl-4'-demethyl-anhydro-homoharringtonine (220 mg, 0.36 mmol) resulting from Example 6 in dry dichloromethane (1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.64 ml, 3.24 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (9.5 ml) and the temperature was raised to 20°C. After stirring at
- 10 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 17.4 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (6g),
- 15 dichloromethane then dichloromethane / methanol, 99:1 to 97:3) to provide the expected compound (103 mg, 50%). The product thus obtained showed the following characteristics:

HRMS calcd for $C_{31}H_{44}NO_9$ $[M + H]^+$ 574.3016, obsd 574.3012

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IR (film) (cm^{-1}): 3519 (OH), 3430 (OH), 1735 (CO_2), 1655 (C=C-O), 1504 (Ar), 1224 (C-O), 1182 (C-O), 1109 (C-O), 1039 (C-O), 910.

1H NMR 400 MHz ($CDCl_3$) (δ ppm, J Hz):

- 25 6.63 (1H, s, H-17*), 6.56 (1H, s, H-14*), 5.96 (1H, d, $J_{3,4} = 9.8$, H-3), 5.86 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 4.88 (1H, m, $J = 6.2$, $OCH(CH_3)_2$), 3.78 (1H, d, $J_{4,3} = 9.8$, H-4), 3.68 (3H, s, OCH_3), 3.54 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.95 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J_{AB} = 14.0$, $J = 6.7$, H-11 α), 2.19 and 1.87 (2H, 2d, $J_{AB} = 16.0$, CH_2CO_2), 2.02 (1H, m, H-6 α), 1.91

(1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.5 – 1.16 (6H, m, 3×CH₂), 1.18 (12H, m, OCH(CH₃)₂ + 2×CH₃).

2°) Method B

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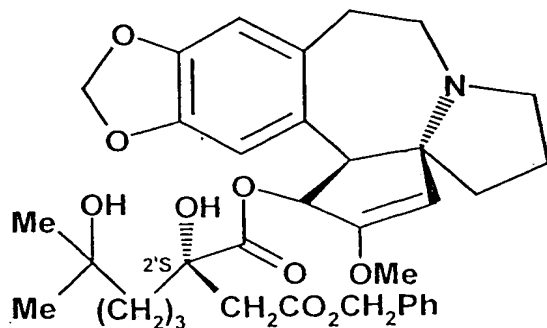
Sodium hydride 60 % (13 mg, 0.325 mmol) was added (in 2 parts, at t = 0 and t = 16 hours) to a solution of homoharringtonine (440 mg, 0.807 mmol) in isopropanol (6 ml) with stirring at ambient temperature under argon. 4 hours after the last addition the mixture was adjusted to pH 1.9 by addition of hydrochloric acid 0.1N (157 ml) and the aqueous layer was washed with ether (3 x 8 ml). The resulting aqueous layer was alkalized with ammonia 25% (0.3 ml) and was extracted with dichloromethane (8 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (311 mg crude, 67%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 61:39). After removal of methanol in vacuo the resulting aqueous layer was alkalized to pH 10 with ammonia 25% and extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (143 mg; 31%). The product thus obtained showed identical characteristics to this obtained with method A.

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Example 28

Preparation of (2'S)-4'-benzyl-4'-demethyl-epi-homoharringtonine :

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To a stirred solution of 4'-benzyl-4'-demethyl-anhydro-epi-homoharringtonine (28 mg, 0.046 mmol) resulting from Example 7 in dry dichloromethane (0.14 ml) under nitrogen was added at -10°C a commercial

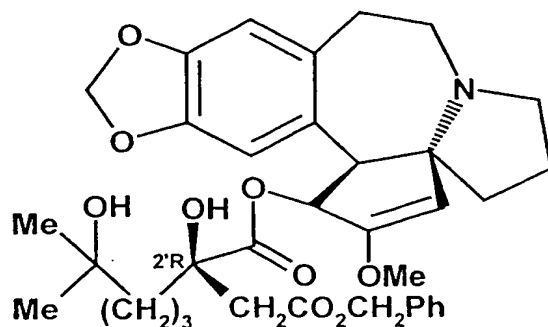
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solution of hydrobromic acid in acetic acid (83 μ l, 0.417 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (2 ml) and the temperature was raised to 20°C . After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 4 ml) up to pH 8. The resulting aqueous layer, after
 5 saturation with sodium chloride, was extracted with dichloromethane (3 x 3 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (30 mg crude, 100%). The crude product thus obtained showed the following characteristics:

10 ^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz) :
 7.34 (5H, m, Ph), 6.64 (1H, s, H-17), 6.60 (1H, s, H-14), 5.90 (3H, m, OCH_2O + H-3), 5.12 and 5.07 (2H, 2d, $J_{\text{AB}} = 12.4$, OCH_2Ph), 5.01 (1H, s, H-1), 3.78 (1H, d, H-4), 3.60 (3H, s, OCH_3), 3.13 (2H, m, H-11 β + H-8 α), 2.96 (1H, m, H-10 α), 2.66 and 2.57 (2H, 2d, $J_{\text{AB}} = 16.7$, CH_2CO_2), 2.60 (2H, m, H-8 β + H-10 β), 2.40 (1H, m,
 15 H-11 α), 2.04 (1H, m, H-6 α), 1.92 (1H, m, H-6 β), 1.78 (2H, m, CH_2 -7), 1.6 - 0.8 (6H, m, $3 \times \text{CH}_2$), 1.16 (3H, s, CH_3), 1.15 (3H, s, CH_3).

Example 29

20 Preparation of (2'R)-4'-benzyl-4'-demethyl-homoharringtonine :



1°) Method A

25

To a stirred solution of 4'-benzyl-4'-demethyl-anhydro-homoharringtonine (261 mg, 0.432 mmol) resulting from Example 8 in dry dichloromethane (1.3 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.775 ml, 3.89 mmol, HBr 30% w/w). After stirring at -10°C for 3
 30 hours, was added water (18.6 ml) and the temperature was raised to 20°C . After

stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 37 ml) up to pH 8. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting
5 crude product was purified by column chromatography (silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99:1 to 95:5) to provide the expected compound (80 mg, 30%). The crude product thus obtained showed the following characteristics:

10 IR (film) (cm^{-1}): 3520 (OH), 3401 (OH), 1744 (CO₂), 1655 (C=C-O), 1504 (Ar), 1224 (C-O), 1173 (C-O), 1082 (C-O), 1037 (C-O), 910.

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

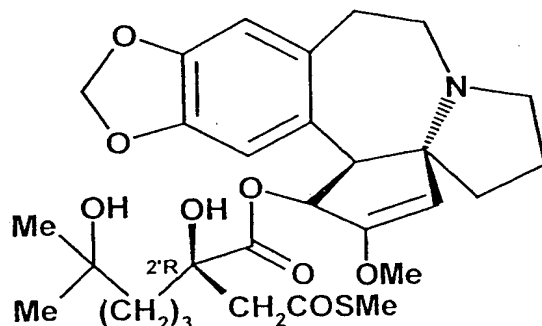
7.33 (5H, m, Ph), 6.62 (1H, s, H-17), 6.44 (1H, s, H-14), 5.96 (1H, d, $J_{3,4}$ = 9.7, H-3), 5.77 and 5.65 (2H, 2s, OCH₂O), 5.09 and 4.94 (2H, 2d, J_{AB} = 12.4, OCH₂Ph),
15 5.05 (1H, s, H-1), 3.70 (1H, d, $J_{4,3}$ = 10, H-4), 3.68 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.93 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.40 (1H, dd, J_{AB} = 14, J = 6.7, H-11 α), 2.31 and 1.92 (2H, 2d, J_{AB} = 16.3, CH₂CO₂), 2.0 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.6 - 1.1
20 (6H, m, 3 \times CH₂), 1.25 (1H, s, OH), 1.19 (3H, s, CH₃), 1.18 (3H, s, CH₃).

2)° Method B

Sodium hydride 60 % (10 mg, 0.275 mmol) was added to a solution of
25 homoharringtonine (300 mg, 0.55 mmol) in benzylic alcohol (4 ml) and the resulting mixture was stirred at ambient temperature for 1.5 hours under argon. After adjusting to pH 2.5 by addition of hydrochloric acid 0.1N (15 ml) the aqueous layer was washed with ether (3 x 15 ml). The resulting aqueous layer was alkalized with ammonia 25% (1.5 ml) and was extracted with dichloromethane
30 (6 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 47:53). After removal of methanol in vacuo the resulting aqueous layer was alkalized to pH 9 with ammonia 25% and extracted with dichloromethane (3 x 5
35 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (154 mg; 45%). The product thus obtained showed the following characteristics:

Example 30

Preparation of (2'R)-4'-methylthio-4'-demethoxy-homoharringtonine :



5

To a stirred solution of 4'-methylthio-4'-demethoxy-anhydro-homoharringtonine (209 mg, 0.384 mmol) resulting from Example 9 in dry dichloromethane (1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.608 ml, 3.46 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (12.2 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 29 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by reversed-phase column chromatography (n-octadecylsilane, 15 µm (20 g), methanol / buffer pH 3, 32:68) and the retained fractions were combined. After removal of methanol in vacuo the residual aqueous layer (250 ml) was adjusted to pH 8, extracted with dichloromethane (3 x 80 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (100 mg, 46.5%). The crude product thus obtained showed the following characteristics:

25 **HRMS** calcd for $C_{29}H_{40}NO_6S$ $[M + H]^+$ 562.2475, obsd 562.2477

IR (film) (cm^{-1}) : 3513 (OH), 3369 (OH), 1744 (CO₂), 1688 (COS), 1655 (C=C-O), 1503 (Ar), 1223 (C-O), 1150 (C-O), 1081 (C-O), 1035 (C-O), 911.

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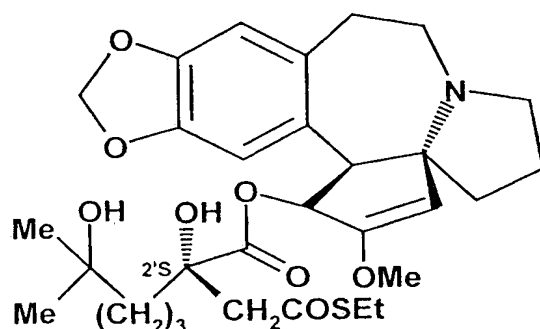
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17*), 6.54 (1H, s, H-14*), 6.01 (1H, d, J_{3,4} = 9.7, H-3), 5.87 (2H, s, OCH₂O), 5.05 (1H, s, H-1), 3.78 (1H, d, J_{4,3} = 9.6, H-4), 3.68 (3H, s, OCH₃), 3.42 (1H, s, 2'-OH), 3.09 (2H, m, H-11β + H-8α), 2.94 (1H, m, H-10α), 2.59 (2H, m, H-8β + H-10β), 2.50 and 2.03 (2H, 2d, J_{AB} = 15.8, CH₂COS), 2.40 (1H, m, H-11α), 2.23 (3H, s, SCH₃), 2.03 (1H, m, H-6_A), 1.91 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.6 – 1.2 (6H, m, 3×CH₂), 1.19 (3H, s, CH₃), 1.18 (3H, s, CH₃).

Example 31

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Preparation of (2'S)-4'-ethylthio-4'-demethoxy-epi-homoharringtonine :



15 To a stirred solution of 4'-ethylthio-4'-demethoxy-anhydro-epi-homoharringtonine (18 mg, 0.032 mmol) resulting from Example 10 in dry dichloromethane (90 μl) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (58 μl, 0.29 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (2 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 2 ml) up to pH 8. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 2 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (18 mg crude, 76%). The crude product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.66 (1H, s, H-17*), 6.59 (1H, s, H-14*), 5.95 and 5.85 (2H, 2d, J_{AB} = 1.2, OCH₂O), 5.95 (1H, d, J_{3,4} = 9.7, H-3), 5.03 (1H, s, H-1), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.66 (3H, s, OCH₃), 3.43 (1H, s, 2'-OH), 3.12 (2H, m, H-11β + H-8α), 2.94 (1H,

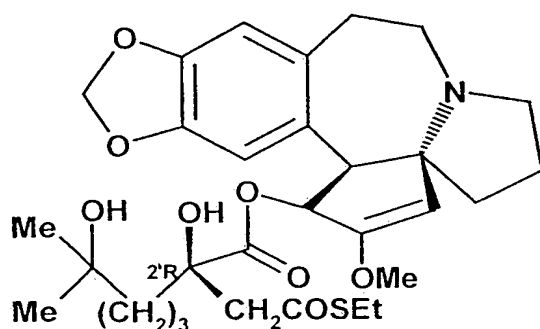
30

m, H-10 α), 2.89 (2H, m, SCH₂CH₃), 2.79 (2H, m, CH₂COS), 2.58 (2H, m, H-8 β + H-10 β), 2.40 (1H, dd, J_{AB} = 14.2, J = 6.9, H-11 α), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.5 - 0.6 (6H, m, 3 \times CH₂), 1.24 (3H, t, J = 7.4, SCH₂CH₃), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃).

5

Example 32

Preparation of (2'R)-4'-ethylthio-4'-demethoxy-homoharringtonine :



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To a stirred solution of 4'-ethylthio-4'-demethoxy-anhydro-homoharringtonine (251 mg, 0.45 mmol) resulting from Example 11 in dry dichloromethane (1.1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.803 ml, 4.05 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (14.6 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 35.9 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (8g), dichloromethane then dichloromethane / methanol, 99.5:0.5 to 95:5) to provide the expected compound (120 mg, 46%). The product thus obtained showed the following characteristics:

25

HRMS calcd for C₃₀H₄₂NO₈S [M + H]⁺ 576.2631, obsd 576.2624

IR (film) (cm⁻¹) : 3514 (OH), 3391 (OH), 1744 (CO₂), 1687 (COS), 1656 (C=C-O), 1504 (Ar), 1223 (C-O), 1159 (C-O), 1081 (C-O), 1035 (C-O), 911.

30

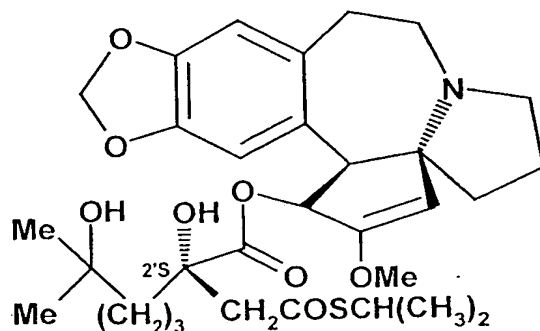
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.63 (1H, s, H-17*), 6.54 (1H, s, H-14*), 5.99 (1H, d, J₃₋₄ = 9.8, H-3), 5.97 (2H, s, OCH₂O), 5.05 (1H, s, H-1), 3.78 (1H, d, J₄₋₃ = 9.8, H-4), 3.67 (3H, s, OCH₃), 3.43 (1H, s, 2'-OH), 3.09 (2H, m, H-11β + H-8α), 2.94 (1H, m, H-10α), 2.84 (2H, m, SCH₂CH₃), 2.59 (2H, m, H-8β + H-10β), 2.46 and 1.98 (2H, 2d, J_{AB} = 15.8, CH₂COS), 2.38 (1H, dd, J_{AB} = 14.0, J = 6.9, H-11α), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.5 – 1.1 (6H, m, 3×CH₂), 1.21 (3H, t, J = 7.5, SCH₂CH₃), 1.19 (3H, s, CH₃), 1.18 (3H, s, CH₃).

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Example 33

Preparation of (2'S)-4'-isopropylthio-4'-demethoxy-epi-homoharringtonine :



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To a stirred solution of 4'-isopropylthio-4'-demethoxy-anhydro-epi-homoharringtonine (28 mg, 0.049 mmol) resulting from Example 12 in dry dichloromethane (0.14 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (88 μl, 0.44 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (2 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 4 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 3 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (19 mg crude, 66%). The crude product thus obtained showed the following characteristics:

25

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

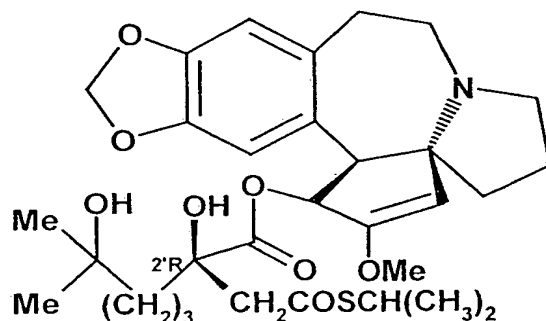
6.65 (1H, s, H-17), 6.59 (1H, s, H-14), 5.94 (1H, d, J₃₋₄ = 10.0, H-3), 5.94 and 5.88 (2H, 2d, J_{AB} = 1.4, OCH₂O), 5.03 (1H, s, H-1), 3.78 (1H, d, J₄₋₃ = 9.7, H-4),

30

3.66 (3H, s, OCH₃), 3.64 (1H, m, CH(CH₃)₂), 3.41 (1H, s, OH), 3.11 (2H, m, H-11β + H-8α), 2.96 (1H, m, H-10α), 2.77 (2H, m, CH₂COS), 2.59 (2H, m, H-8β + H-10β), 2.40 (1H, dd, J_{AB} = 14.2, J = 6.9, H-11α), 2.04 (1H, m, H-6A), 1.90 (1H, m, H-6B), 1.76 (2H, m, CH₂-7), 1.7 - 0.6 (6H, m, 3×CH₂), 1.29 and 1.27 (6H, 2d, J = 6.8, CH(CH₃)₂), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃).

Example 34

Preparation of (2'R)-4'-isopropylthio-4'-demethoxy-homoharringtonine :



To a stirred solution of 4'-isopropylthio-4'-demethoxy-anhydro-homoharringtonine (267 mg, 0.467 mmol) resulting from Example 13 in dry dichloromethane (1.1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.839 ml, 4.2 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (15.6 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 38.2 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μm (8g), dichloromethane then dichloromethane / methanol, 99:1) to provide the expected compound (118 mg, 43%). The product thus obtained showed the following characteristics:

HRMS calcd for C₃₁H₄₄NO₈S [M + H]⁺ 590.2788, obsd 590.2789

IR (film) (cm⁻¹) : 3521 (OH), 3385 (OH), 1743 (CO₂), 1681 (COS), 1656 (C=C-O), 1504 (Ar), 1223 (C-O), 1159 (C-O), 1082 (C-O), 1039 (C-O), 910.

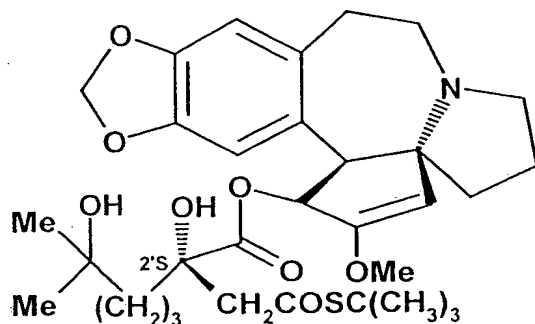
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.64 (1H, s, H-17), 6.55 (1H, s, H-14), 5.97 (1H, d, J_{3,4} = 9.8, H-3), 5.88 (2H, s, OCH₂O), 5.05 (1H, s, H-1), 3.79 (1H, d, J_{4,3} = 9.8, H-4), 3.67 (3H, s, OCH₃), 3.56 (1H, m, J = 6.9, CH(CH₃)₂), 3.44 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.95 (1H, td, J = 11.1 and 6.8, H-10α), 2.59 (2H, m, H-8β + H-10β), 2.40 and 1.92 (2H, 2d, J_{AB} = 15.6, CH₂COS), 2.38 (1H, dd, J_{AB} = 13.9, J = 6.7, H-11α), 2.02 (1H, m, H-6A), 1.90 (1H, m, H-6B), 1.76 (2H, m, CH₂-7), 1.6 - 1.1 (6H, m, 3×CH₂), 1.27 and 1.25 (6H, 2d, J = 6.9, CH(CH₃)₂), 1.18 (6H, 2s, 2×CH₃).

10

Example 35

Preparation of (2'S)-4'-tert-butylthio-4'-demethoxy-epi-homoharringtonine :



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To a stirred solution of 4'-tert-butylthio-4'-demethoxy-anhydro-epi-homoharringtonine (60 mg, 0.102 mmol) resulting from Example 14 in dry dichloromethane (0.3 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.183 ml, 0.44 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (3 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 8.6 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 8 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (30 mg crude, 48%). The crude product thus obtained showed the following characteristics:

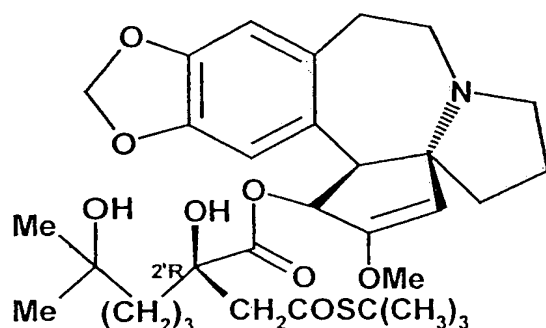
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.65 (1H, s, H-17), 6.59 (1H, s, H-14), 5.96 and 5.89 (2H, 2d, J = 1.3, OCH₂O), 5.96 (1H, d, J_{3,4} = 9.9, H-3), 5.03 (1H, s, H-1), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.66

(3H, s, OCH₃), 3.39 (1H, s, 2'-OH), 3.13 (2H, m, H-11β + H-8α), 2.96 (1H, m, H-10α), 2.74 (2H, m, CH₂COS), 2.62 (2H, m, H-8β + H-10β), 2.41 (1H, dd, J_{AB} = 14.0, J = 6.7, H-11α), 2.04 (1H, m, H-6_A), 1.91 (1H, m, H-6_B), 1.71 (2H, m, CH₂-7), 1.6 – 0.8 (6H, m, 3×CH₂), 1.44 (9H, s, C(CH₃)₃), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃).

Example 36

Preparation of (2'R)-4'-*tert*-butylthio-4'-demethoxy-homoharringtonine :



To a stirred solution of 4'-*tert*-butylthio-4'-demethoxy-anhydro-homoharringtonine (216 mg, 0.37 mmol) resulting from Example 15 in dry dichloromethane (1.1 ml) under nitrogen was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.658 ml, 3.33 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (12.6 ml) and the temperature was raised to 20°C. After stirring at 20°C for 3 hours, was added a sodium carbonate solution (0.76 M, 31.5 ml) up to pH 8-9. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 30 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μm (8g), dichloromethane then dichloromethane / methanol, 99:1 to 95:5) to provide the expected compound (70 mg, 31.5%). The crude product thus obtained showed the following characteristics:

HRMS calcd for C₃₂H₄₆NO₈S [M + H]⁺ 604.2944, obsd 604.2940

IR (film) (cm⁻¹) : 3514 (OH), 3369 (OH), 1744 (CO₂), 1679 (COS), 1655 (C=C-O), 1504 (Ar), 1223 (C-O), 1159 (C-O), 1081 (C-O), 1035 (C-O), 910.

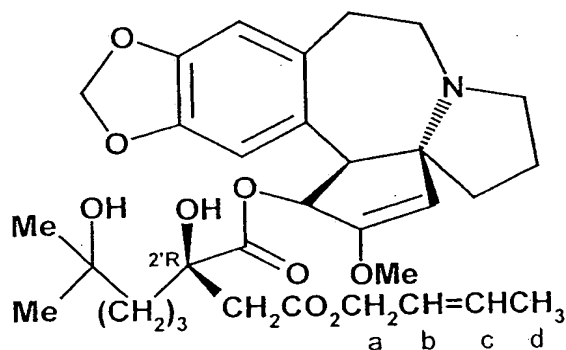
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz) :

6.65 (1H, s, H-17), 6.54 (1H, s, H-14), 5.96 (1H, d, $J_{3,4} = 9.7$, H-3), 5.89 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 3.78 (1H, d, $J_{4,3} = 9.9$, H-4), 3.67 (3H, s, OCH_3), 3.46 (1H, s, 2'-OH), 3.09 (2H, m, H-11 β + H-8 α), 2.95 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.32 and 1.81 (2H, 2d, $J_{AB} = 15.5$, CH_2COS), 2.38 (1H, m, H-11 α), 2.03 (1H, m, H-6 α), 1.91 (1H, m, H-6 β), 1.76 (2H, m, CH_2 -7), 1.6 – 1.1 (6H, m, $3 \times \text{CH}_2$), 1.42 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.18 (3H, s, CH_3), 1.175 (3H, s, CH_3).

Example 37

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Preparation of (2'R)-4'-(but-2-enyl)-4'-demethyl-homoharringtonine :



15 Sodium hydride 60% (15 mg, 0.366 mmol) was added to a solution of homoharringtonine (500 mg, 0.917 mmol) in crotyl alcohol (1 ml) and the resulting mixture was stirred at ambient temperature for 2.5 hours. After adjusting to pH 4 by addition of hydrochloric acid 1N the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized with ammonia 25% and was

20 extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (454 mg crude, 70%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 55:45). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 9.2 with

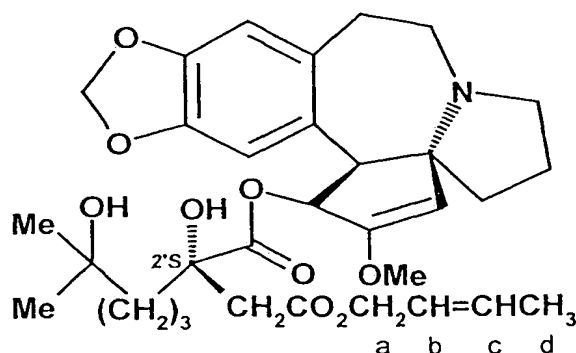
25 ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (122 mg; 30%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17*), 6.54 (1H, s, H-14*), 5.98 (1H, d, J_{3,4} = 9.8, H-3), 5.86 and 5.85 (2H, 2d, J_{AB} = 1.5, OCH₂O), 5.74 (1H, m, H-c), 5.53 (1H, m, H-b), 5.05 (1H, s, H-1), 4.46 and 4.35 (2H, 2dd, J_{AB} = 12.3, J_{a-b} = 6.5, CH₂-a), 3.77 (1H, d, J_{4,3} = 9.8, H-4), 3.68 (3H, s, OCH₃), 3.55 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.94 (1H, m, H-10α), 2.58 (2H, m, H-8β + H-10β), 2.38 (1H, m, H-11α), 2.25 and 1.90 (2H, 2d, J_{AB} = 16.4, CH₂CO₂), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.72 (3H, dd, J_{d-c} = 6.6, J_{d-b} = 1.2, CH₃-d), 1.39 (6H, m, 3×CH₂), 1.18 (6H, 2s, 2×CH₃).

Example 38

Preparation of (2'S)-4'-(but-2-enyl)-4'-demethyl-epi-homoharringtonine :



Sodium hydride 60% (15 mg, 0.366 mmol) was added to a solution of homoharringtonine (500 mg, 0.917 mmol) in crotyl alcohol (5 ml) and the resulting mixture was stirred at ambient temperature for 2 hours. After adjusting to pH 4 by addition of hydrochloric acid 1N the aqueous layer was washed with ether (3 x 10 ml) and diluted with water (50 ml). The resulting aqueous layer was alkalinized to pH 10.6 with ammonia 25% and was extracted with dichloromethane (5 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (456 mg crude, 78%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 65:35). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% and extracted with dichloromethane (56 x 10 ml). The combined organic layers were dried over magnesium sulfate

and evaporated to dryness to provide the expected compound (188 mg; 32%). The product thus obtained showed the following characteristics:

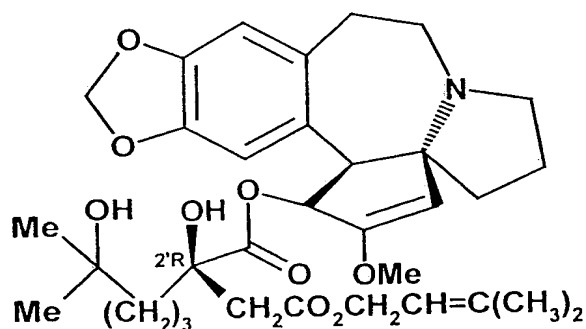
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

- 5 6.64 (1H, s, H-17*), 6.60 (1H, s, H-14*), 5.94 (1H, d, J_{3,4} = 9.7, H-3), 5.94 and 5.85 (2H, 2d, J_{AB} = 1.2, OCH₂O), 5.76 (1H, m, H-c), 5.54 (1H, m, H-b), 5.03 (1H, s, H-1), 4.49 (2H, m, CH₂-a), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.66 (3H, s, OCH₃), 3.53 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.94 (1H, m, H-10α), 2.61 and 2.52 (2H, 2d, J_{AB} = 16.7, CH₂CO₂), 2.59 (2H, m, H-8β + H-10β), 2.39 (1H, dd, J = 14.1 and 6.8, H-11α), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.72 (2H, m, CH₂-7) and 10 (3H, dd, J_{d-c} = 6.5, J_{d-b} = 0.9, CH_{3-d}), 1.20 (3H, m, CH₂), 1.16 (3H, s, CH₃), 1.15 (3H, s, CH₃), 1.06 (1H, m, CH₂), 0.93 (1H, m, CH₂), 0.736 (1H, m, CH₂).

Example 39

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Preparation of (2'R)-4'-(3-methyl-2-butenyl)-4'-demethyl-homoharringtonine :



- 20 Sodium hydride 60 % (29.4 mg, 0.735 mmol) was added to a solution of homoharringtonine (500 mg, 0.917 mmol) in 3-methyl-2-butenol (4 ml) and the resulting mixture was stirred at ambient temperature for 1.5 hours under argon. After adjusting to pH 2.5 by addition of hydrochloric acid 0.1N (15 ml) the aqueous layer was washed with ether (3 x 15 ml). The resulting aqueous layer was
- 25 alkalized with ammonia 25% (1.5 ml) and was extracted with dichloromethane (6 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (464 mg crude, 85%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 47:53). After removal of methanol in vacuo the resulting

aqueous layer was alkalized to pH 9 with ammonia 25% and extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (266 mg; 48%). The product thus obtained showed the following characteristics:

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¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

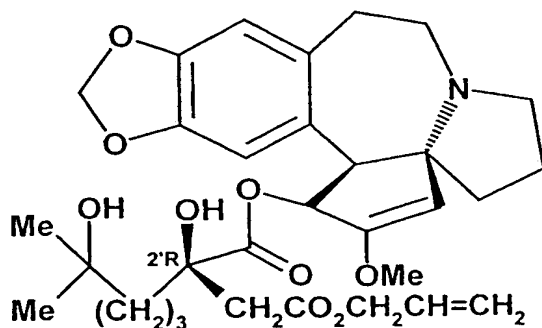
6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, J_{3,4} = 9.8, H-3), 5.86 and 5.84 (2H, 2d, J = 1.5, OCH₂O), 5.28 (1H, m, H-C=), 5.05 (1H, s, H-1), 4.54 and 4.42 (2H, 2dd, J_{AB} = 12.4, J = 7.1, OCH₂), 3.77 (1H, d, J_{4,3} = 9.8, H-4), 3.68 (3H, s, OCH₃), 3.54 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.94 (1H, dt, J = 11.5 and 7.0, H-10α), 2.58 (2H, m, H-8β + H-10β), 2.38 (1H, dd, J_{AB} = 14.0, J = 6.7, H-11α), 2.24 and 1.89 (2H, 2d, J_{AB} = 16.4, CH₂CO₂), 2.04 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.77 (2H, m, CH₂-7), 1.75 (3H, s, CH₃-C=), 1.68 (3H, s, CH₃-C=), 1.39 (6H, m, 3xCH₂), 1.19 (3H, s, CH₃), 1.18 (3H, s, CH₃).

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Example 40

Preparation of (2'R)-4'-(2-propenyl)-4'-demethyl-homoharringtonine :

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Sodium hydride 60 % (29.8 mg, 0.745 mmol) was added to a solution of homoharringtonine (508 mg, 0.932 mmol) in 2-propenol (5 ml) and the resulting mixture was stirred at ambient temperature for 2 hours under argon. After adjusting to pH 2.1 by addition of hydrochloric acid 0.1N (17 ml) the aqueous layer was washed with ether (3 x 15 ml). The resulting aqueous layer was alkalized with ammonia 25% (1.5 ml) and was extracted with dichloromethane (6 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (417 mg crude, 78%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g),

30

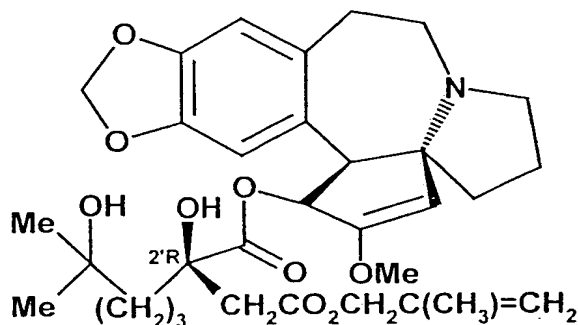
buffer pH 3 / methanol, 61.5:38.5). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 10 with ammonia 25% and extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (289 mg; 54%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.99 (1H, d, J_{3,4} = 9.8, H-3), 5.87 (1H, m, HC=), 5.85 (2H, m, OCH₂O), 5.30 (1H, m, J = 17.2, =CH₂), 5.22 (1H, m, J = 10.4, =CH₂), 5.05 (1H, s, H-1), 4.53 and 4.42 (2H, 2m, J_{AB} = 13.3, J = 5.6, OCH₂), 3.77 (1H, d, J_{4,3} = 9.8, H-4), 3.68 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.94 (1H, dt, J = 11.0 and 6.9, H-10α), 2.59 (2H, m, H-8β + H-10β), 2.38 (1H, dd, J_{AB} = 14.0, J = 6.7, H-11α), 2.28 and 1.90 (2H, 2d, J_{AB} = 16.5, CH₂CO₂), 2.05 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.5 – 1.1 (6H, m, 3xCH₂), 1.29 (1H, s, 4''-OH), 1.19 (6H, 2s, 2xCH₃).

Example 41

20 Preparation of (2'R)-4'-(2-methyl-2-propenyl)-4'-demethyl-homoharringtonine :



Sodium hydride 60 % (23.5 mg, 0.470 mmol) was added to a solution of homoharringtonine (400 mg, 0.734 mmol) in 2-methyl-2-propenol (4 ml) and the resulting mixture was stirred at ambient temperature for 2 hours under argon. After adjusting to pH 2 by addition of hydrochloric acid 0.1N (15 ml) the aqueous layer was washed with ether (3 x 8 ml). The resulting aqueous layer was alkalinized with ammonia 25% (0.3 ml) and was extracted with dichloromethane (4 x 8 ml). The combined organic layers were dried over magnesium sulfate and

evaporated to dryness (302 mg crude, 70%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 55:45). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 9.8 with ammonia 25% (0.9 ml) and
 5 extracted with dichloromethane (5 \times 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (183 mg; 43%). The product thus obtained showed the following characteristics:

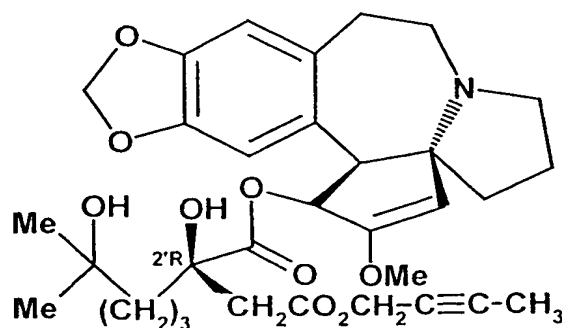
10 ^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, $J_{3-4} = 9.8$, H-3), 5.85 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 4.96 and 4.91 (2H, 2s, $=\text{CH}_2$), 4.47 and 4.33 (2H, 2d, $J_{AB} = 13.3$, OCH_2), 3.77 (1H, d, $J_{4-3} = 9.8$, H-4), 3.68 (3H, s, OCH_3), 3.51 (1H, s, 2'-OH), 3.09 (2H, m, H-11 β + H-8 α), 2.94 (1H, dt, $J = 11.0$ and 6.8 , H-10 α), 2.59
 15 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J_{AB} = 14.0$, $J = 6.7$, H-11 α), 2.30 and 1.92 (2H, 2d, $J_{AB} = 16.5$, CH_2CO_2), 2.02 (1H, m, H-6 $_A$), 1.90 (1H, m, H-6 $_B$), 1.75 (2H, m, CH_2 -7), 1.73 (3H, s, CH_3 -C=), 1.5 – 1.1 (6H, m, $3 \times \text{CH}_2$), 1.19 (6H, 2s, $2 \times \text{CH}_3$).

Example 42

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Preparation of (2'R)-4'-(2-butynyl)-4'-demethyl-homoharringtonine:



25 Sodium hydride 60 % (30 mg, 0.75 mmol) was added (in 5 parts, at $t = 0$, $t = 1.5$, $t = 3.5$, $t = 5$ and $t = 24$ hours) to a solution of homoharringtonine (510 mg, 0.936 mmol) in 2-butynol (2.9 ml) with stirring at ambient temperature under argon. 2 hours after the last addition the mixture was adjusted to pH 2.1 by addition of hydrochloric acid 0.1N (17 ml) and the aqueous layer was washed with
 30 ether (3 \times 10 ml). The resulting aqueous layer was alkalinized with ammonia 25%

(0.3 ml) and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (368 mg crude, 67.5%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 5 65:35). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 10 with ammonia 25% (0.4 ml) and extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (171 mg; 46.5%). The product thus obtained showed the following characteristics:

10

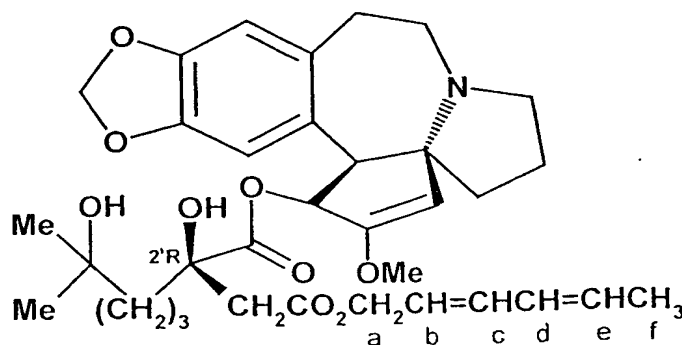
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.99 (1H, d, $J_{3,4} = 9.5$, H-3), 5.94 and 5.87 (2H, 2d, $J_{AB} = 1.5$, OCH_2O), 5.05 (1H, s, H-1), 4.60 and 4.48 (2H, 2dq, $J_{AB} = 15.2$, $J = 2.4$, OCH_2), 3.77 (1H, d, $J_{4,3} = 9.8$, H-4), 3.67 (3H, s, OCH_3), 3.51 (1H, s, 2'-OH), 3.09 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J_{AB} = 13.9$, $J = 6.7$, H-11 α), 2.30 and 1.88 (2H, 2d, $J_{AB} = 16.5$, CH_2CO_2), 2.02 (1H, m, H-6 $_A$), 1.88 (1H, m, H-6 $_B$), 1.86 (3H, t, $J = 2.4$, $\text{CH}_3\text{-C}\equiv$), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.5 – 1.1 (6H, m, $3\times\text{CH}_2$), 1.19 (3H, s, CH_3), 1.18 (3H, s, CH_3).

20

Example 43

Preparation of (2'R)-4'-(hexa-2,4-dienyl)-4'-demethyl-homoharringtonine :



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Sodium hydride 60 % (8.8 mg, 0.22 mmol) was added to a solution of homoharringtonine (300 mg, 0.55 mmol) in (*E,E*)-hexa-1,4-dienol (3 ml) and the resulting mixture was stirred at 35 °C for 1 h 45 min under argon. After adjusting

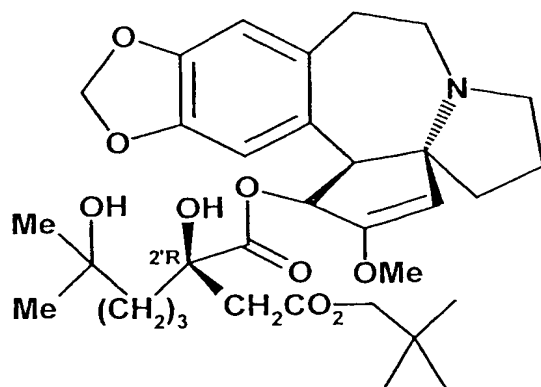
to pH 1.9 by addition of hydrochloric acid 0.1N (9 ml) the aqueous layer was washed with ether (3 x 6 ml). The resulting aqueous layer was alkalized to pH 10 with ammonia 25% (0.3 ml) and was extracted with dichloromethane (4 x 6 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (224 mg crude, 67%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 40:60). After removal of methanol *in vacuo* the resulting aqueous layer was washed with ether (10 ml), alkalized to pH 9.5 with ammonia 25% (0.3 ml) and extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (175 mg; 43%). The product thus obtained showed the following characteristics:

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.53 (1H, s, H-14), 6.22 (1H, dd, $J_{c-b} = 15.2$, $J_{c-d} = 10.5$, H-c), 6.06 (1H, ddd, $J_{d-e} = 15.0$, $J_{d-c} = 10.6$, $J_{d-f} = 1.4$, H-d), 5.98 (1H, d, $J_{3-4} = 9.8$, H-3), 5.84 and 5.83 (2H, 2d, $J_{AB} = 1.5$, OCH_2O), 5.76 (1H, dq, $J_{e-d} = 15.0$, $J_{e-f} = 6.8$, H-e), 5.56 (1H, dt, $J_{b-c} = 15.3$, $J_{b-a} = 6.6$, H-b), 5.05 (1H, s, H-1), 4.53 and 4.42 (2H, 2dd, $J_{AB} = 12.8$, $J_{a-b} = 6.6$, $\text{CH}_2\text{-a}$), 3.70 (1H, d, $J_{4-3} = 9.8$, H-4), 3.67 (3H, s, OCH_3), 3.52 (1H, s, 2'-OH), 3.09 (2H, m, H-11 β +H-8 α), 2.94 (1H, dt, $J = 11.5$ and 6.9, H-10 α), 2.58 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J_{AB} = 14.0$, $J = 6.7$, H-11 α), 2.26 and 1.88 (2H, 2d, $J_{AB} = 16.4$, CH_2CO_2), 2.02 (1H, m, H-6 α), 1.90 (1H, m, H-6 β), 1.77 (3H, d, $J \sim 6$, $\text{CH}_3\text{-f}$) and (2H, m, $\text{CH}_2\text{-7}$), 1.5 – 1.1 (6H, m, 3 \times CH_2), 1.28 (1H, s, 4''OH), 1.19 (3H, s, CH_3), 1.18 (3H, s, CH_3).

Example 44

Preparation of (2'R)-4'-(methylcyclopropyl)methyl-4'-demethyl-homoharringtonine :



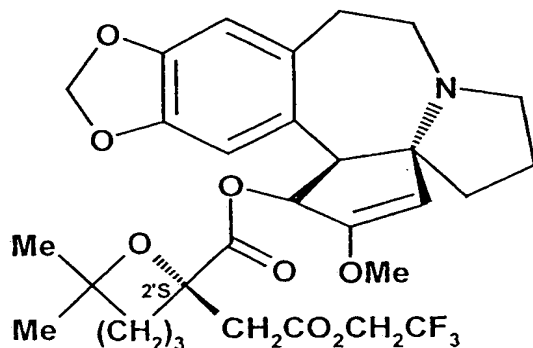
Sodium hydride 60 % (3.8 mg, 0.095 mmol) was added to a solution of homoharringtonine (263 mg, 0.482 mmol) in (1-methylcyclopropyl)methanol (2.3 ml) and the resulting mixture was stirred at ambient temperature for 20 h under argon. After adjusting to pH 2 by addition of hydrochloric acid 0.1N (9 ml) the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalized to pH 9.5 with ammonia 25% (0.3 ml) and was extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (231 mg crude, 80%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 50:50). After removal of methanol in vacuo the resulting aqueous layer was alkalized to pH 9.5 with ammonia 25% (0.4 ml) and extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (173 mg; 69%). The product thus obtained showed the following characteristics:

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.99 (1H, d, $J_{3,4} = 9.6$, H-3), 5.86 (2H, s, OCH_2O), 5.06 (1H, s, H-1), 3.86 and 3.72 (2H, 2d, $J_{AB} = 11.2$, $\text{CH}_2\text{-a}$), 3.78 (1H, d, $J_{4,3} = 9.6$, H-4), 3.68 (3H, s, OCH_3), 3.53 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.95 (1H, m, H-10 α), 2.58 (2H, m, H-8 β + H-10 β), 2.39 (1H, dd, $J_{AB} = 14.0$, $J = 6.7$, H-11 α), 2.28 and 1.95 (2H, 2d, $J_{AB} = 16.3$, CH_2CO_2), 2.02 (1H, m, H-6 α), 1.90 (1H, m, H-6 β), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.5 – 1.1 (6H, m, 3x CH_2), 1.29 (1H, s, 4''-OH), 1.19 (6H, 2s, 2x CH_3), 1.09 (3H, s, $\text{CH}_3\text{-c}$), 0.44 and 0.35 (4H, 2m, $\text{CH}_2\text{-d,e}$).

Example 45

Preparation of (-)-cephalotaxyl (2'S)-2-(2,2,2-trifluoro-ethoxy)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-(2,2,2-trifluoroethyl)-4'-demethyl-anhydro-epi-homoharringtonine :



To a stirred mixture of 4'-demethyl-anhydro-epi-homoharringtonine (1 g, 1.947 mmol) in dry dichloromethane (10 ml) under argon was added at 0°C triethylamine (dried over potassium hydroxide) (270 μ l, 1.947 mmol) and 2,4,6-trichlorobenzoyl chloride (305 μ l, 1.947 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (476 mg, 3.896 mmol) and 2,2,2-trifluoroethanol (280 μ l, 3.899 mmol) in dry dichloromethane (3 ml) was added. After stirring at ambient temperature for 20 hours, the reaction mixture was diluted with dichloromethane (19 ml). The resulting organic layer was successively washed with water (27 ml), with saturated sodium hydrogen carbonate solution (27 ml), with brine (27 ml). After a last extraction of the combined aqueous layers with dichloromethane (27 ml) the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (10g), dichloromethane then dichloromethane / methanol, 99:1 to 80:20) to provide the expected compound (838 mg, 72%). The product thus obtained showed the following characteristics:

25

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

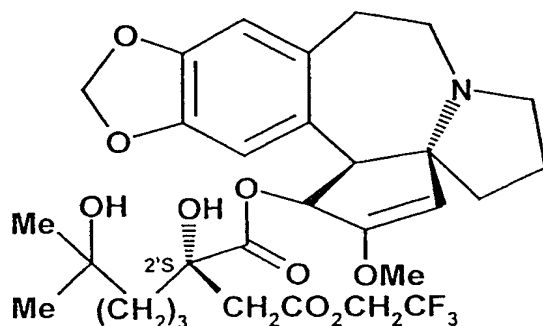
6.61 (1H, s, H-14*), 6.57 (1H, s, H-17*), 5.83 (3H, m, H-3 + OCH₂O), 5.02 (1H, s, H-1), 4.43 and 4.33 (2H, 2dq, J_{AB} = 12.7, J_{H-F} = 8.6, OCH₂CF₃), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.65 (3H, s, OCH₃), 3.23 (1H, m, H-11 β), 3.09 (1H, m, H-8 α), 2.94

(1H, dt, $J = 11.6$ and 7.2 , H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.39 (1H, m, H-11 α), 2.18 and 1.84 (2H, 2d, $J_{AB} = 14.5$, CH_2CO_2), 2.01 (1H, m, H-6 α), 1.89 (1H, m, H-6 β), 1.74 (2H, m, CH_2 -7), 1.5 – 1.2 (6H, m, $3 \times \text{CH}_2$), 1.10 (3H, s, CH_3), 1.03 (3H, s, CH_3).

5

Example 46

Preparation of (2'S)-4'-(2,2,2-trifluoroethyl)-4'-demethyl-epi-homoharringtonine :



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To a stirred solution of 4'-(2,2,2-trifluoroethyl)-4'-demethyl-anhydro-epi-homoharringtonine (300 mg, 0.504 mmol) resulting from Example 45 in dry dichloromethane (1.55 ml) under argon was added at -10°C a commercial solution of hydrobromic acid in acetic acid (0.903 ml, 4.53 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (14 ml) and the temperature was raised to 20°C . After stirring at 20°C for 2.75 hours, was added a sodium carbonate solution (0.76 M, 25 ml) up to pH 8.7. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 11.4 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μm (15g), dichloromethane / methanol, 99:1 to 90:10) to provide the expected compound (211 mg, 68%). The product thus obtained showed the following characteristics:

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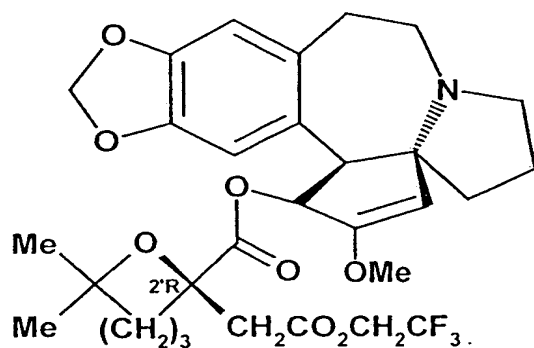
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.65 (1H, s, H-17*), 6.60 (1H, s, H-14*), 5.94 and 5.85 (2H, 2d, $J_{AB} = 1.3$, OCH_2O), 5.93 (1H, d, H-3), 5.05 (1H, s, H-1), 4.53 and 4.32 (2H, 2dq, $J_{AB} = 12.6$, $\text{JH-F} = 8.4$, OCH_2CF_3), 3.79 (1H, d, $J_{4-3} = 9.6$, H-4), 3.65 (3H, s, OCH_3), 3.36 (1H,

s, 2'-OH), 3.08 (2H, m, H-11 β + H-8 α), 2.93 (1H, m, H-10 α), 2.70 and 2.64 (2H, 2d, J_{AB} = 16.8, CH₂CO₂), 2.57 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, J_{AB} = 14.0, J = 6.8, H-11 α), 2.01 (1H, m, H-6 α), 1.89 (1H, m, H-6 β), 1.76 (2H, m, CH₂-7), 1.34 (1H, s, 4''-OH), 1.3 – 1.15 (3H, m, CH₂), 1.17 (3H, s, CH₃), 1.16 (3H, s, CH₃), 1.03 (1H, m, CH₂), 0.97 (1H, m, CH₂), 0.70 (1H, m, CH₂).

Example 47

Preparation of (-)-cephalotaxyl (2'R)-2-(2,2,2-trifluoro-ethoxy)carbonylmethyl-6,6-dimethyl-2-tetrahydropyrane carboxylate or 4'-(2,2,2-trifluoroethyl)-4'-demethyl-anhydro-homoharringtonine



To a stirred mixture of 4'-demethyl-anhydro-homoharringtonine (723 mg, 1.407 mmol) in dry dichloromethane (5.1 ml) under argon was added at 0°C triethylamine (dried over potassium hydroxide) (196 μ l, 1.408 mmol) and 2,4,6-trichlorobenzoyl chloride (220 μ l, 1.407 mmol) over a period of 10 minutes. After stirring at ambient temperature for 2.5 hours a solution of 4-dimethylaminopyridine (344 mg, 2.816 mmol) and 2,2,2-trifluoroethanol (202 μ l, 2.813 mmol) in dry dichloromethane (2.2 ml) was added. After stirring at ambient temperature for 17 hours, the reaction mixture was diluted with dichloromethane (14 ml). The resulting organic layer was successively washed with water (19 ml), with saturated sodium hydrogen carbonate solution (19 ml), with brine (19 ml). After a last extraction of the combined aqueous layers with dichloromethane (19 ml) the combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting crude product was purified by column chromatography (silica 15-40 μ m (10g), dichloromethane / methanol, 99:1 to 90:10) to provide the expected compound (523 mg, 77%). The product thus obtained showed the following characteristics:

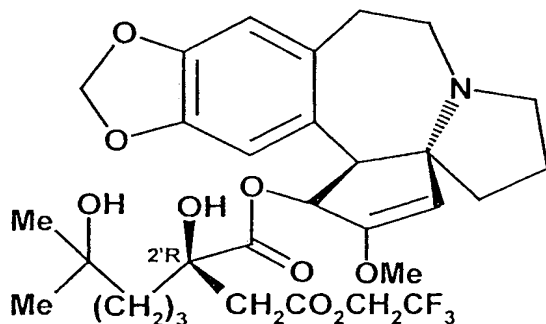
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.58 (1H, s, H-14), 5.88 (1H, d, H-3), 5.86 and 5.79 (2H, 2d, J_{AB} = 1.4, OCH₂O), 5.05 (1H, s, H-1), 4.41 and 4.35 (2H, 2m, OCH₂CF₃), 3.80 (1H, d, J_{4,3} = 9.7, H-4), 3.70 (3H, s, OCH₃), 3.12 (2H, m, H-11β) + H-8α), 2.96 (1H, m, H-10α), 2.60 (2H, m, H-8β + H-10β), 2.37 (1H, dd, J = 14.1 and 6.7, H-11α), 2.20 and 1.68 (2H, 2d, J_{AB} = 14.7, CH₂CO₂), 2.01 (1H, m, H-6_A), 1.93 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.7 – 1.2 (6H, m, 3×CH₂), 1.10 (3H, s, CH₃), 1.04 (3H, s, CH₃).

Example 48

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Preparation of (2'R)-4'-(2,2,2-trifluoroethyl)-4'-demethyl-homoharringtonine :



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To a stirred solution of 4'-(2,2,2-trifluoroethyl)-4'-demethyl-anhydro-homoharringtonine (507 mg, 0.851 mmol) resulting from Example 47 in dry dichloromethane (2.6 ml) under argon was added at -10°C a commercial solution of hydrobromic acid in acetic acid (1.525 ml, 7.659 mmol, HBr 30% w/w). After stirring at -10°C for 3 hours, was added water (24 ml) and the temperature was raised to 20°C. After stirring at 20°C for 2.75 hours, was added a sodium carbonate solution (0.76 M, 44 ml) up to pH 8.5. The resulting aqueous layer, after saturation with sodium chloride, was extracted with dichloromethane (3 x 19 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness (508 mg crude, 97%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 60:40 to 20:80). After removal of methanol *in vacuo* the resulting aqueous layer was alkalized to pH 9.6 with ammonia 25% (0.4 ml) and extracted with dichloromethane (12 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected

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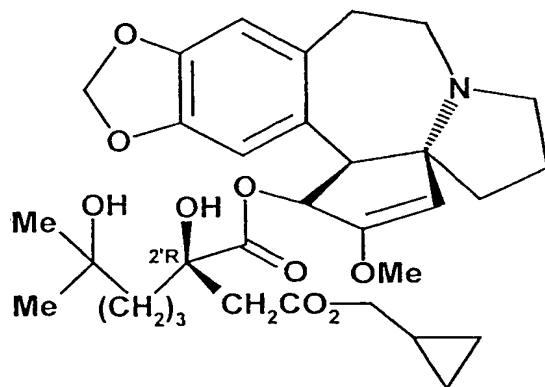
compound (122 mg; 23%). The product thus obtained showed the following characteristics:

^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

- 5 6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.99 (1H, d, $J_{3-4} = 9.7$, H-3), 5.86 and 5.84 (2H, 2d, $J_{AB} = 1.2$, OCH_2O), 4.42 and 4.26 (2H, 2dd, $J_{AB} = 12.7$, $J_{H-F} = 8.4$, OCH_2CF_3), 5.05 (1H, s, H-1), 3.78 (1H, d, $J_{4-3} = 9.8$, H-4), 3.68 (3H, s, OCH_3), 3.45 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.96 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.39 (1H, m, H-11 α), 2.37 and 1.93 (2H, 2d, $J_{AB} = 16.5$, CH_2CO_2), 2.03 (1H, m, H-6 $_A$), 1.92 (1H, m, H-6 $_B$), 1.76 (2H, m, CH_2 -7), 1.55 - 1.15 (6H, m, $3 \times \text{CH}_2$), 1.25 (1H, s, 4''-OH), 1.19 (6H, 2s, $2 \times \text{CH}_3$).
- 10

Example 49

- 15 Preparation of (2'R)-4'-cyclopropylmethyl-4'-demethyl-homoharringtonine :



- Sodium hydride 60 % (3.2 mg, 0.08 mmol) was added to a solution of homoharringtonine (210 mg, 0.385 mmol) in cyclopropylmethanol (1.53 ml) and the resulting mixture was stirred at ambient temperature for 2.5 h under argon. After adjusting to pH 1.8 by addition of hydrochloric acid 0.1N (6 ml) the aqueous layer was washed with ether (3 x 5 ml). The resulting aqueous layer was alkalized to pH 9.5 with ammonia 25% (0.3 ml) and was extracted with dichloromethane (6 x 5 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (175 mg crude, 78%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 57:43). After removal of
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- 25

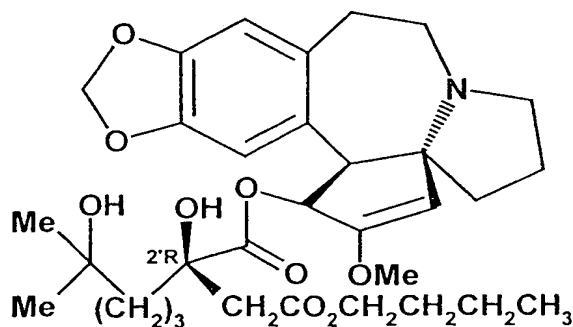
methanol *in vacuo* the resulting aqueous layer was alkalized to pH 9.5 with ammonia 25% (0.4 ml) and extracted with dichloromethane (6 × 6 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (170 mg; 51%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.98 (1H, d, J_{3,4} = 9.8, H-3), 5.87 and 5.86 (2H, 2d, J_{AB} = 1.3, OCH₂O), 5.06 (1H, s, H-1), 3.83 and 3.77 (2H, 2dd, J_{AB} = 11.4, J_{a-b} = 1.3, CH₂-a), 3.78 (1H, d, J_{4,3} ~ 10, H-4), 3.68 (3H, s, OCH₃), 3.55 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.95 (1H, m, H-10α), 2.61 (2H, m, H-8β + H-10β), 2.39 (1H, dd, J_{AB} = 14.1, J = 6.8, H-11α), 2.27 and 1.93 (2H, 2d, J_{AB} = 16.3, CH₂CO₂), 2.03 (1H, m, H-6_A), 1.93 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.5 – 1.1 (6H, m, 3×CH₂), 1.19 (3H, s, CH₃), 1.18 (3H, s, CH₃), 1.06 (1H, m, H-b), 0.55 and 0.24 (4H, 2m, CH₂-c,d).

Example 50

Preparation of (2'R)-4'-butyl-4'-demethyl-homoharringtonine:



Sodium hydride 60 % (4.95 mg, 0.124 mmol) was added to a solution of homoharringtonine (225 mg, 0.4125 mmol) in *n*-butanol (2.25 ml) and the resulting mixture was stirred at ambient temperature for 20 hours under argon. After adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (6 ml) the aqueous layer was washed with ether (3 × 6 ml). The resulting aqueous layer was alkalized to pH 10 with ammonia 25% (0.43 ml) and was extracted with dichloromethane (10 × 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (178 mg crude, 74%). The crude

product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (100 g), buffer pH 3 / methanol, 50:50). After removal of methanol *in vacuo* the resulting aqueous layer was alkalized to pH 9.5 with ammonia 25% (0.4 ml) and extracted with dichloromethane (8 \times 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (107 mg; 44%). The product thus obtained showed the following characteristics:

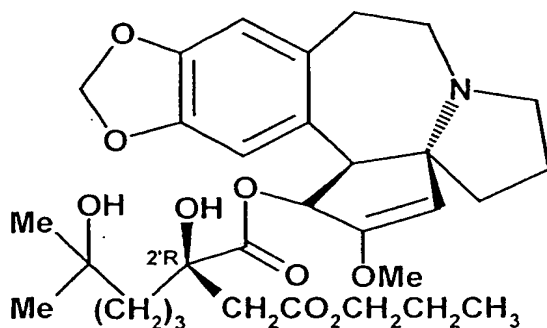
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

- 10 6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.98 (1H, d, $J_{3-4} = 9.7$, H-3), 5.86 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 4.02 and 3.92 (2H, 2dt, $J_{AB} = 10.8$, $J_{a-b} = 6.8$, $\text{CH}_2\text{-a}$), 3.78 (1H, d, $J_{4-3} = 9.8$, H-4), 3.68 (3H, s, OCH_3), 3.52 (1H, s, 2'-OH), 3.11 (2H, m, H-11 β +H-8 α), 2.95 (1H, m, H-10 α), 2.60 (2H, m, H-8 β +H-10 β), 2.39 (1H, dd, $J = 14.1$ and 6.8 , H-11 α), 2.25 and 1.92 (2H, 2d, $J_{AB} = 16.3$, CH_2CO_2), 2.03 (1H, m, H-6 α), 1.92 (1H, m, H-6 β), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.55 (2H, m, $\text{CH}_2\text{-b}$), 1.45 - 1.15 (8H, m, $\text{CH}_2\text{-c}$ and $3 \times \text{CH}_2$), 1.19 (3H, s, CH_3), 1.18 (3H, s, CH_3), 0.92 (3H, t, $J = 7.3$, $\text{CH}_3\text{-d}$)

Example 51

20

Preparation of (2'R)-4'-propyl-4'-demethyl-homoharringtonine :



- 25 Sodium hydride 60 % (8.9 mg, 0.223 mmol) was added to a solution of homoharringtonine (405 mg, 0.742 mmol) in *n*-propanol (4 ml) and the resulting mixture was stirred at ambient temperature for 1.5 h under argon. After adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (12 ml) the aqueous layer was washed with ether (3 \times 8 ml). The resulting aqueous layer was alkalized to pH
- 30 9.6 with ammonia 25% (0.8 ml) and was extracted with dichloromethane (6 \times 10

ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (374 mg crude, 88%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 62:38 to 50:50). After removal of methanol *in vacuo* the resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% (0.8 ml) and extracted with dichloromethane (6 \times 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (244 mg; 57%). The product thus obtained showed the following characteristics:

10

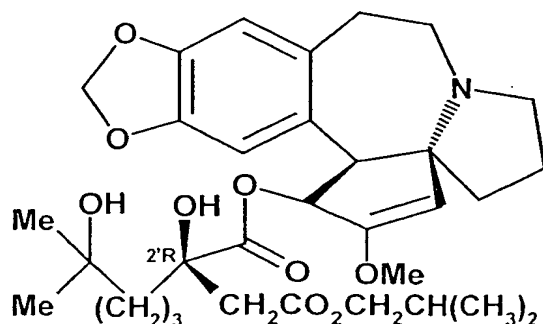
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, $J_{3-4} = 9.7$, H-3), 5.86 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 3.97 and 3.89 (2H, 2dt, $J_{AB} = 10.6$, $J_{a-b} = 6.8$, $\text{CH}_2\text{-a}$), 3.78 (1H, d, $J_{4-3} = 9.8$, H-4), 3.68 (3H, s, OCH_3), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J = 14.0$ and 6.7 , H-11 α), 2.25 and 1.92 (2H, 2d, $J_{AB} = 16.3$, CH_2CO_2), 2.02 (1H, m, H-6 α), 1.90 (1H, m, H-6 β), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.60 (2H, m, $\text{CH}_2\text{-b}$), 1.5 - 1.1 (6H, m, $3 \times \text{CH}_2$), 1.19 (3H, s, CH_3), 1.18 (3H, s, CH_3), 0.91 (3H, t, $J = 7.4$, $\text{CH}_3\text{-c}$)

20

Example 52

Preparation of (2'R)-4'-isobutyl-4'-demethyl-homoharringtonine :



25

Sodium hydride 60 % (8.8 mg, 0.220 mmol) was added to a solution of homoharringtonine (3975 mg, 0.7282 mmol) in iso-butanol (4 ml) and the resulting mixture was stirred at ambient temperature for 1.5 h under argon. After adjusting to pH 1.8 by addition of hydrochloric acid 0.1N (11 ml) the aqueous layer was washed with ether (3 \times 8 ml). The resulting aqueous layer was alkalinized to pH

30

9.7 with ammonia 25% and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (316 mg crude, 768%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (135 g), buffer pH 3 / methanol, 50:50). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (254 mg; 61%). The product thus obtained showed the following characteristics:

10

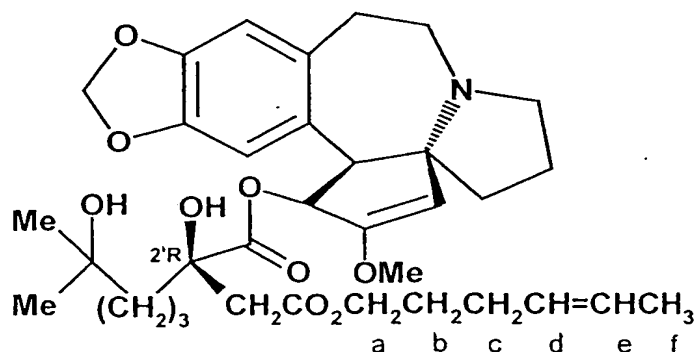
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.98 (1H, d, $J_{3,4} = 9.5$, H-3), 5.86 (2H, s, OCH_2O), 5.06 (1H, s, H-1), 3.81 and 3.71 (2H, 2dt, $J_{AB} = 10.7$, $J_{a,b} = 6.7$, $\text{CH}_2\text{-a}$), 3.78 (1H, d, $J_{4,3} = 9.5$, H-4), 3.68 (3H, s, OCH_3), 3.52 (1H, s, 2'-OH), 3.11 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, $J = 14.1$ and 6.8 , H-11 α), 2.26 and 1.94 (2H, 2d, $J_{AB} = 16.3$, CH_2CO_2), 2.04 (1H, m, H-6 α), 1.90 (1H, m, H-6 β), 1.85 (1H, m, H-b), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.5 - 1.15 (6H, m, $3 \times \text{CH}_2$), 1.19 (6H, 2s, $2 \times \text{CH}_3$), 0.91 (3H, d, $J_{c,b} = 6.8$, $\text{CH}_3\text{-c}$), 0.90 (3H, d, $J_{d,b} = 6.8$, $\text{CH}_3\text{-d}$).

20

Example 53

Preparation of (2'R)-4'-(hex-4-enyl)-4'-demethyl-homoharringtonine :



25

Sodium hydride 60 % (10.96 mg, 0.274 mmol) was added to a solution of homoharringtonine (374 mg, 0.685 mmol) in 4-hexenol (4 ml) and the resulting mixture was stirred at ambient temperature for 45 min under argon. After adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (12 ml) the aqueous

layer was washed with ether (3 x 8 ml). The resulting aqueous layer was alkalinized to pH 10 with ammonia 25% and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (358 mg crude, 85%). The crude product thus obtained
 5 was purified by phase-reversed chromatography (octadecylsilane 12 μ m (135 g), buffer pH 3 / methanol, 30:70). After removal of methanol *in vacuo* the resulting aqueous layer was washed with ether (5 ml), dichloromethane (5 ml), alkalinized to pH 9.5 with ammonia 25% (0.8 ml) and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and
 10 evaporated to dryness to provide the expected compound (226 mg; 54%). The product thus obtained showed the following characteristics:

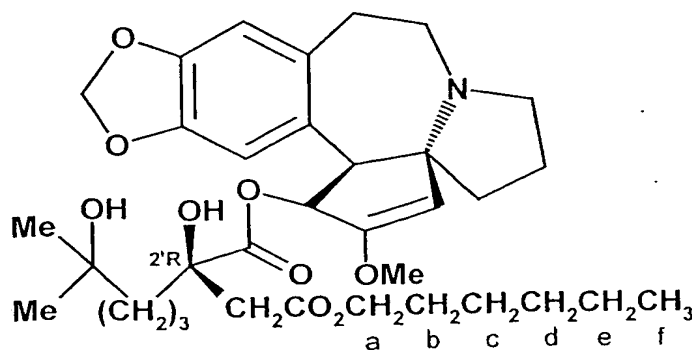
^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, $J_{3,4} = 9.7$, H-3), 5.85 (2H, s, OCH₂O), 5.42 (2H, m, H-e,d), 5.05 (1H, s, H-1), 3.99 and 3.92 (2H, 2m, CH₂-a),
 15 3.78 (1H, d, $J_{4,3} = 9.7$, H-4), 3.68 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.59 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, J = 14.0 and 6.7, H-11 α), 2.24 and 1.92 (2H, 2d, $J_{AB} = 16.2$, CH₂CO₂), 2.0 (3H, m, H-6_A and CH₂-c), 1.92 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.63 (5H, m, CH₂-b and
 20 CH₃-f), 1.5 - 1.1 (6H, m, 3xCH₂), 1.18 (6H, 2s, 2xCH₃).

Example 54

Preparation of (2'R)-4'-hexyl-4'-demethyl-homoharringtonine :

25



Sodium hydride 60 % (6.6 mg, 0.16 mmol) was added to a solution of homoharringtonine (300 mg, 0.55 mmol) in *n*-hexanol (3 ml) and the resulting

mixture was stirred at ambient temperature for 1.5 hours under argon. After adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (5 ml) the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% and was extracted with dichloromethane (6 x 10 ml).
 5 The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (135 g), buffer pH 3 / methanol, 30:70). After removal of methanol *in vacuo* and adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (5 ml), the resulting aqueous layer was washed with ether
 10 (3x5 ml), alkalinized to pH 9.5 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (158 mg; 47%). The product thus obtained showed the following characteristics:

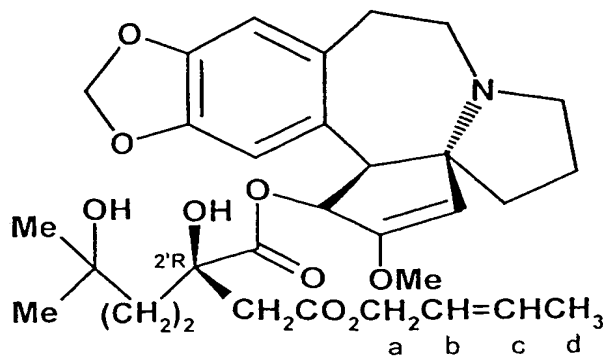
15 ^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.98 (1H, d, $J_{3,4} = 9.8$, H-3), 5.86 (2H, s, OCH_2O), 5.05 (1H, s, H-1), 4.0 and 3.91 (2H, 2m, $\text{CH}_2\text{-a}$), 3.78 (1H, d, $J_{4,3} = 9.9$, H-4), 3.68 (3H, s, OCH_3), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.39 (1H, dd, $J = 13.8$ and 6.7 , H-11 α), 2.25 and 1.92 (2H, 2d, $J_{AB} = 16.2$, CH_2CO_2), 2.17 (1H, m, H-6 $_A$), 1.92 (1H, m, H-6 $_B$), 1.76 (2H, m, $\text{CH}_2\text{-7}$), 1.56 (2H, m, $\text{CH}_2\text{-b}$), 1.5 - 1.1 (12H, m, $\text{CH}_2\text{-c,d,e}$ and $3\times\text{CH}_2$), 1.19 (3H, s, CH_3), 1.18 (3H, s, CH_3), 0.89 (3H, t, $J = 6.83$, $\text{CH}_3\text{-f}$)

Example 55

25

Preparation of (2'R)-4'-(but-2-enyl)-4'-demethyl-harringtonine :

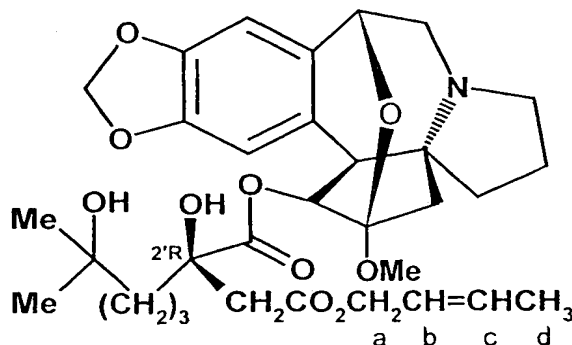


Sodium hydride 60% (7.4 mg, 0.188 mmol) was added to a solution of harringtonine (250 mg, 0.471 mmol) in crotyl alcohol (2.5 ml) and the resulting mixture was stirred at ambient temperature for 2.5 hours. After adjusting to pH 4 by addition of hydrochloric acid 1N the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized with ammonia 25% and was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (268 mg crude, 99.50%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 65:35 to 60:40). After removal of methanol *in vacuo* the resulting aqueous layer was alkalinized to pH 9.2 with ammonia 25% and extracted with dichloromethane (6 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (157 mg; 58.5%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):
 6.62 (1H, s, H-17), 6.55 (1H, s, H-14), 5.98 (1H, d, J_{3,4} = 9.7, H-3), 5.85 (2H, s, OCH₂O), 5.75 (1H, dq, J_{c-b} = 15.3, J_{c-d} = 6.4, H-c), 5.55 (1H, dtq, J_{b-c} = 15.3, J_{b-a} = 6.4, J_{b-d} = 1.7, H-b), 5.07 (1H, s, H-1), 4.47 and 4.35 (2H, 2dd, J_{AB} = 12.3, J_{a-b} = 6.5, CH₂-a), 3.78 (1H, d, J₄₋₃ = 9.6, H-4), 3.70 (3H, s, OCH₃), 3.63 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.95 (1H, m, H-10 α), 2.58 (2H, m, H-8 β + H-10 β), 2.398 (1H, m, H-11 α), 2.28 and 1.89 (2H, 2d, J_{AB} = 16.4, CH₂CO₂), 2.01 (1H, m, H-6_A), 1.89 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.72 (3H, dd, J_{d-c} = 6.6, J_{d-b} = 1.2, CH₃-d), 1.60 (3H, m, CH₂), 1.25 (1H, m, CH₂), 1.17 (3H, s, CH₃), 1.14 (3H, s, CH₃).

Example 56

Preparation of 4-(2-butenyl) (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate of (-)-drupacine :



Sodium hydride 60% (14 mg, 0.358 mmol) was added to a solution of 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate of (-)-drupacine
 5 (500 mg, 0.8 mmol) in crotyl alcohol (4.5 ml) and the resulting mixture was stirred at ambient temperature for 2.5 hours. After adjusting to pH 4 by addition of hydrochloric acid 1N the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized with ammonia 25% and was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over
 10 magnesium sulfate and evaporated to dryness (366 mg crude, 74%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 57:43). After removal of methanol *in vacuo* the resulting aqueous layer was alkalinized to pH 10.6 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined
 15 organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (132 mg; 27%). The product thus obtained showed the following characteristics:

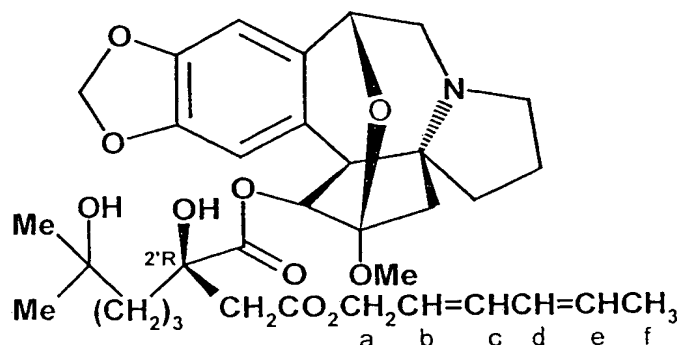
$^1\text{H NMR}$ 400 MHz (CDCl_3) (δ ppm, J Hz):

20 6.65 (1H, s, H-17*), 6.46 (1H, s, H-14*), 5.90 and 5.87 (2H, 2d, $J_{AB} = 1.5$, OCH_2O), 5.79 (1H, m, H-c), 5.57 (1H, m, H-b), 5.23 (1H, d, $J_{3-4} = 9.6$, H-3), 4.86 (1H, d, $J_{11-10A} = 4.3$, H-11), 4.56 and 4.45 (2H, 2dd, $J_{AB} = 12.3$, $J_{a-b} = 6.6$, $\text{CH}_2\text{-a}$), 3.56 (1H, d, $J_{4-3} = 9.6$, H-4), 3.51 (1H, s, 2'-OH), 3.41 (3H, s, OCH_3), 3.12 (1H, dd, $J_{AB} = 13.2$, $J_{10A-11} = 4.9$, H-10_A), 3.08 (1H, m, H-8 α), 2.97 (1H, d, $J_{AB} = 13.1$, H-10_B), 2.67 (1H, d, $J_{AB} = 14.0$, H-1A), 2.40 (1H, ~q, $J = 8.7$, H-8 β), 2.29 and 1.96 (2H, 2d, $J_{AB} = 16.4$, CH_2CO_2), 2.19 (1H, m, H-6_A), 2.04 (1H, m, H-6_B), 1.9 – 1.1 (8H, m, $\text{CH}_2\text{-7}$ and $3\times\text{CH}_2$), 1.73 (3H, dd, $J_{d-c} = 6.5$, $J_{d-b} = 1.1$, $\text{CH}_3\text{-d}$), 1.55 (1H, d, $J_{AB} = 14.0$, H-1_B), 1.18 (3H, s, CH_3), 1.16 (3H, s, CH_3).

Example 57

Preparation of 4-(hexa-2,4-dienyl) (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate of (-)-drupacine :

5



Sodium hydride 60% (6.8 mg, 0.272 mmol) was added to a solution of 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate of (-)-drupacine
 10 (200 mg, 0.34 mmol) in hexa-2,4-dienol (2 ml) and the resulting mixture was stirred at ambient temperature for 2 hours. After adjusting to pH 1.5 by addition of hydrochloric acid 1N (7 ml) the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% and was extracted with dichloromethane (5 x 10 ml). The combined organic layers
 15 were dried over magnesium sulfate and evaporated to dryness (182 mg crude, 86%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 40:60). After removal of methanol *in vacuo* the resulting aqueous layer was adjusted to pH 1.5 with hydrochloric acid 1N, washed with ether (3x10 ml), alkalinized to pH
 20 10.6 with ammonia 25% and extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (50 mg; 23.5%). The product thus obtained showed the following characteristics:

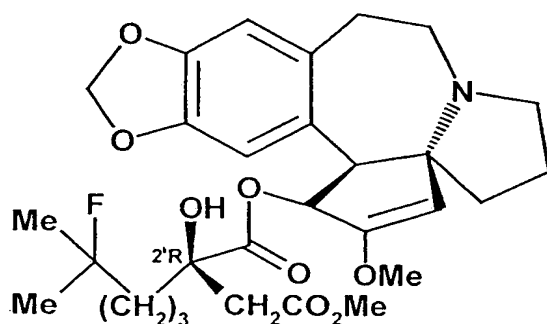
25 ^1H NMR 400 MHz (CDCl_3) (δ ppm, J Hz):

6.65 (1H, s, H-17*), 6.46 (1H, s, H-14*), 6.26 (1H, dd, $J_{c-b} = 15.2$, $J_{c-d} = 10.5$, H-c),
 6.05 (1H, m, H-d) , 5.88 and 5.85 (2H, 2d, $J_{AB} = 1.3$, OCH_2O), 5.76 (1H, m, H-e) ,
 5.60 (1H, m, H-b) , 5.23 (1H, d, $J_{3-4} = 9.6$, H-3), 4.86 (1H, d, $J_{11-10A} = 4.3$, H-11),
 4.63 and 4.52 (2H, 2dd, $J_{AB} = 12.9$, $J_{a-b} = 6.6$, $\text{CH}_2\text{-a}$), 3.55 (1H, d, $J_{4-3} = 9.6$, H-4),
 30 3.51 (1H, s, 2'-OH), 3.41 (3H, s, OCH_3), 3.11 (1H, dd, $J_{AB} = 13.3$, $J_{10A-11} = 4.9$, H-

10_A), 3.06 (1H, m, H-8_α), 2.96 (1H, d, J_{AB} = 13.1, H-10_B), 2.66 (1H, d, J_{AB} = 14.0, H-1A), 2.42 (1H, m, H-8_β), 2.30 and 1.96 (2H, 2d, J_{AB} = 16.5, CH₂CO₂), 2.19 (1H, m, H-6_A), 2.05 (1H, m, H-6_B), 1.77 (2H, m, CH₂-7) and (3H, d, J_{I-e} = 6.2, CH₃-f), 1.6 – 1.1 (6H, m, 3xCH₂), 1.55 (1H, d, J_{AB} = 14.0, H-1_B), 1.17 (3H, s, CH₃), 1.16 (3H, s, CH₃).

Example 58

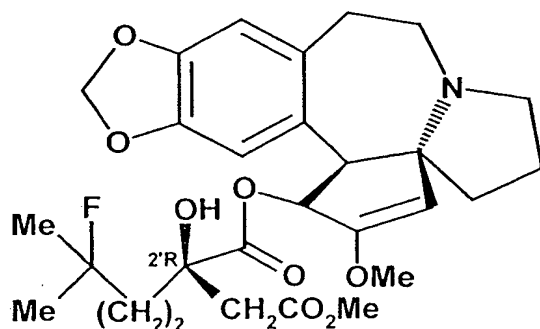
Preparation of (2'R)-4"-Fluoro-4"-deoxy-homoharringtonine :



To a stirred solution of homoharringtonine (20 mg, 0.037 mmol) in dry dichloromethane (1.5 ml) under nitrogen was slowly added DAST (25 μ l, 0.185 mmol) at -40°C. After stirring at -20°C for 3 hours, was added a saturated sodium hydrogen carbonate solution (2 ml), the resulting aqueous layer was extracted with dichloromethane (3 x 5 ml) and the combined organic layers were washed with water (5 ml), with brine (5ml), were dried over magnesium sulfate and evaporated to dryness. The resulting crude product (13 mg) was purified by column chromatography (silica 15-40 μ m (0.2g), dichloromethane then dichloromethane / methanol, 98:2) to provide the expected compound (4 mg, 20%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz) :

6.63 (1H, s, H-17), 6.54 (1H, s, H-14), 6.08 (1H, d, J_{3,4} = 9.3, H-3), 5.87 and 5.86 (2H, 2d J_{AB} = 1.4, OCH₂O), 5.04 (1H, s, H-1), 3.77 (1H, d, J_{4,3} = 9.8, H-4), 3.67 (3H, s, OCH₃), 3.57 (3H, s, OCH₃), 3.39 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, m, J = 14 and 6.8, H-11 α), 2.26 and 1.89 (2H, 2d, J_{AB} = 16.4, CH₂CO₂), 2.02 (1H, m, H-6_A), 1.91 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.6 – 1.2 (6H, m, 3xCH₂), 1.34 (3H, d, J_{H-F} = 21.4, CH₃), 1.28 (3H, d, J_{H-F} = 21.4, CH₃).

Example 59Preparation of (2'R)-3"-Fluoro-3"-deoxy-harringtonine :

5

To a stirred solution of harringtonine (50 mg, 0.094 mmol) in dry dichloromethane (3.5 ml) under nitrogen was slowly added DAST (62 μ l, 0.47 mmol) at -40°C . After stirring at -20°C for 3 hours, was added a saturated sodium hydrogen carbonate solution (5 ml), the resulting aqueous layer was extracted with dichloromethane (3 x 5 ml). The combined organic layers were washed with water (5 ml), with brine (5ml), dried over magnesium sulfate and evaporated to dryness. The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (135 g), buffer pH 3 / methanol, 45:65).

After removal of methanol in vacuo the resulting aqueous layer was adjusted to pH 8.6 with ammonia 25% and extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (11 mg; 22%). The product thus obtained showed the following characteristics:

20

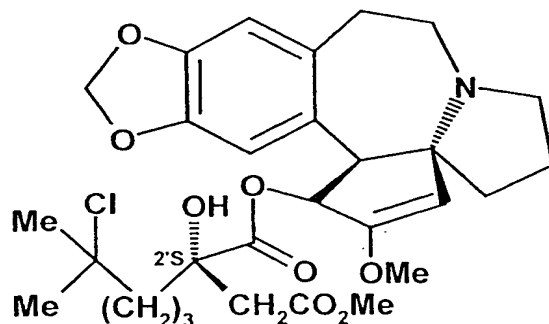
$^1\text{H NMR}$ 400 MHz (CDCl_3) (δ ppm, J Hz):

6.63 (1H, s, H-17), 6.54 (1H, s, H-14), 6.01 (1H, d, $J_{3,4} = 9.8$, H-3), 5.87 and 5.856 (2H, 2d $J_{AB} = 1.4$, OCH_2O), 5.05 (1H, s, H-1), 3.77 (1H, d, $J_{4,3} = 9.8$, H-4), 3.67 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.54 (1H, s, 2'-OH), 3.10 (2H, m, H-11 β + H-8 α), 2.94 (1H, m, H-10 α), 2.60 (2H, m, H-8 β + H-10 β), 2.38 (1H, m, J = 14 and 6.8, H-11 α), 2.29 and 1.90 (2H, 2d, $J_{AB} = 16.6$, CH_2CO_2), 2.03 (1H, m, H-6 α), 1.91 (1H, m, H-6 β), 1.75 (2H, m, CH_2 -7), 1.7 – 1.1 (4H, m, $2 \times \text{CH}_2$), 1.30 (3H, d, $J_{\text{H-F}} = 21.4$, CH_3), 1.29 (3H, d, $J_{\text{H-F}} = 21.4$, CH_3).

25

Example 60

Preparation of (2'S)-4"-Chloro-4"-deoxy-epi-homoharringtonine :



5

To a stirred solution of epi-homoharringtonine (100 mg, 0.18 mmol) in dry chloroform (2 ml) under nitrogen was added SOCl₂ (131 μ l, 1.8 mmol). After stirring at ambient temperature for 2 hours, was added a saturated sodium hydrogen carbonate solution (5 ml), the resulting aqueous layer was extracted with dichloromethane (3 x 5 ml) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (104 mg crude, 100%). The product thus obtained showed the following characteristics:

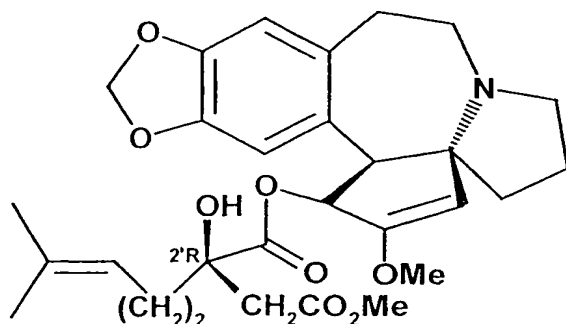
15 ¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.64 (1H, s, H-17), 6.59 (1H, s, H-14), 5.95 and 5.87 (2H, 2d J_{AB} = 1.2, OCH₂O), 5.94 (1H, d, J_{3,4} = 9.8, H-3), 5.04 (1H, s, H-1), 3.78 (1H, d, J_{4,3} = 9.7, H-4), 3.67 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.58 (1H, s, 2'-OH), 3.11 (2H, m, H-11 β + H-8 α), 2.93 (1H, m, H-10 α), 2.62 and 2.54 (2H, 2d, J_{AB} = 16.5, CH₂CO₂), 2.60 (2H, m, H-8 β + H-10 β), 2.39 (1H, m, J = 13.9 and 6.6, H-11 α), 2.02 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.76 (2H, m, CH₂-7), 1.7 – 0.7 (6H, m, 3 \times CH₂), 1.53 (3H, s, CH₃), 1.52 (3H, s, CH₃).

25

Example 61

Preparation of 4-methyl (2R)-2-hydroxy-2-(4-methyl-pent-3-enyl)succinate of (-)-cephalotaxine :



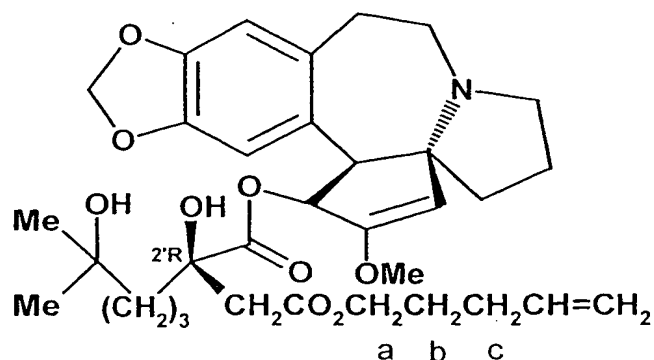
To a stirred solution of homoharringtonine (100 mg, 0.18 mmol) in dry pyridine (2 ml) under nitrogen was added POCl₃ (170 μ l, 1.8 mmol) at -5°C . After stirring at -5°C for 20 hours and adjusting to pH 0.5 by addition of hydrochloric acid 50% (9 ml) the aqueous layer was washed with ether (3 x 10 ml). The resulting aqueous layer was alkalinized to pH 9.5 with ammonia 25% and was extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (100 g), buffer pH 3 / methanol, 45:55). After removal of methanol in vacuo the resulting aqueous layer was adjusted to pH 1.5 with hydrochloric acid 1N, washed with ether (3x10 ml), alkalinized to pH 10.6 with ammonia 25% and extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (20 mg; 21%). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 6.0 (1H, d, $J_{3,4} = 9.8$, H-3), 5.88 and 5.83 (2H, 2d $J_{AB} = 1.4$, OCH₂O), 5.06 (1H, s, H-1), 5.01 (1H, m, =CH), 3.78 (1H, d, $J_{4,3} = 9.8$, H-4), 3.68 (3H, s, OCH₃), 3.58 (3H, s, OCH₃), 3.51 (1H, s, 2'-OH), 3.14 (2H, m, H-11 β + H-8 α), 2.96 (1H, m, H-10 α), 2.39 (2H, m, H-8 β + H-10 β), 2.39 (1H, m, $J = 14.1$ and 6.7 , H-11 α), 2.27 and 1.89 (2H, 2d, $J_{AB} = 16.4$, CH₂CO₂), 2.1 – 1.9 (3H, m, CH₂-6 + CH₂), 2.1 – 1.9 (3H, m, CH₂-7 + CH₂), 1.66 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.42 (2H, m, CH₂).

Example 62

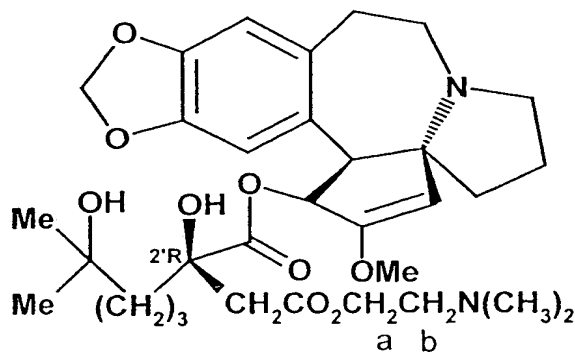
Preparation of (2'R)-4'-(4-pentenyl)-4'-demethyl-homoharringtonine:



Sodium hydride 60 % (7.1 mg, 0.177 mmol) was added to a solution of homoharringtonine (322 mg, 0.590 mmol) in 4-penten-1-ol (3.2 ml) and the resulting mixture was stirred at ambient temperature for 2 hours under argon. After adjusting to pH 1.9 by addition of hydrochloric acid 0.1N (11 ml), the aqueous layer was washed with ether (3 x 6 ml). The resulting aqueous layer was alkalinized with ammonia 25% (five drops) and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (230 mg crude, 65 %). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μ m (135 g), buffer pH 3 / methanol, 50 : 50). After removal of methanol *in vacuo* the resulting aqueous layer was washed with ether (10 ml) and alkalinized to pH 9.5 with ammonia 25% (five drops) and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (149 mg; 42 %). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, $J_{3,4}$ = 9.8, H-3), 5.85 (2H, s, OCH₂O), 5.80 (1H, m, CH=), 5.05 (1H, s, H-1), 5.03 (2H, m, =CH₂), 3.98 (2H, m, CH₂-a), 3.77 (1H, d, $J_{4,3}$ = 9.8, H-4), 3.68 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.12 (2H, m, H-11 β + H-8 α), 2.94 (1H, dt, J = 11.2 and 6.9, H-10 α), 2.58 (2H, m, H-8 β + H-10 β), 2.38 (1H, dd, J_{AB} = 14.0, J = 6.7, H-11 α), 2.25 and 1.92 (2H, 2d, J_{AB} = 16.3, CH₂CO₂), 2.09 (2H, q, J = 7.2, CH₂-c), 2.03 (1H, m, H-6_A), 1.90 (1H, m, H-6_B), 1.75 (2H, m, CH₂-7), 1.67 (2H, qt, J = 7.4, CH₂-b), 1.50 – 1.30 (6H, m, 3 \times CH₂), 1.29 (1H, s, 4''-OH), 1.18 and 1.19 (6H, 2s, 2 \times CH₃).

Example 63Preparation of (2'R)-4'-(dimethylamino-ethyl)-4'-demethyl-homoharringtonine:

5

Sodium hydride 60 % (5.8 mg, 0.145 mmol) was added to a solution of homoharringtonine (400 mg, 0.733 mmol) in N,N-dimethylethanol (4 ml) and the resulting mixture was stirred at ambient temperature for 2 hours under argon.

10 After adjusting to pH 1.5 by addition of hydrochloric acid 0.1N (20 ml), the aqueous layer was washed with ether (3 x 8 ml). The resulting aqueous layer was alkalinized with ammonia 25% (pH = 8-9) and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (quantitative). The crude product thus obtained was

15 purified by phase-reversed chromatography (octadecylsilane 12 μ m (135 g), buffer pH 3 / methanol, 100:0 then 95:5 ; 90:10 ; 80:20). After removal of methanol *in vacuo* the resulting aqueous layer was washed with ether (10 ml) and alkalinized to pH 9.5 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and

20 evaporated to dryness to provide the expected compound (266 mg; 60 %). The product thus obtained showed the following characteristics:

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

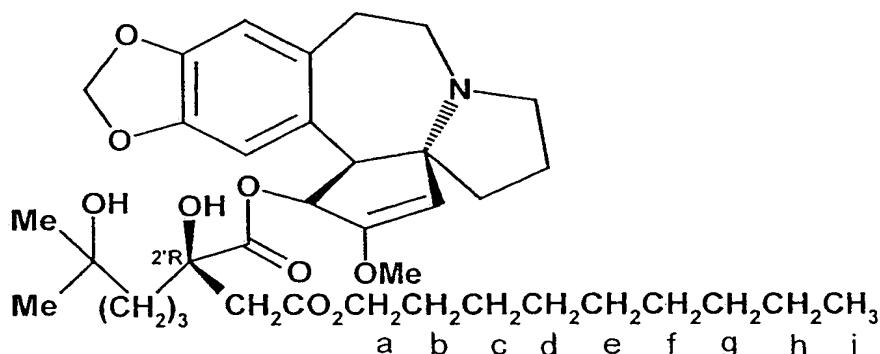
25 6.60 (1H, s, H-17), 6.54 (1H, s, H-14), 6.02 (1H, d, $J_{3,4} = 9.8$, H-3), 5.84 (2H, s, OCH₂O), 5.04 (1H, s, H-1), 4.43 (1H, ddd, $J = 11.8$, $J = 8.0$, $J = 4.0$, H-a α), 3.79 (1H, d, $J_{4,3} = 9.8$, H-4), 3.74 (1H, m, H-a β), 3.67 (3H, s, OCH₃), 3.12 (2H, m, H-11 β +H-8 α), 2.94 (1H, dt, $J = 11.2$ and 6.9 , H-10II), 2.58 (2H, m, H-8I+H-10II), 2.49 (1H, ddd, $J = 12.6$, $J = 8.0$, $J = 4.3$, H-bII), 2.37 (1H, dd, $J_{AB} = 14.3$, $J = 6.7$, H-11 α), 2.34 (1H, m, H-6 α), 2.22 (6H, s, N(CH₃)₂), 2.22 and 2.11 (2H, 2d, $J_{AB} =$

15.5, CH_2CO_2), 2.03 (1H, m, H-6 β), 1.89 (1H, ddd, $J = 12.1$, $J = 7.7$, $J = 4.3$, H-b β), 1.75 (2H, m, CH_2 -7), 1.50 – 1.20 (7H, m, $3 \times \text{CH}_2$ and 4''-OH), 1.19 and 1.18 (6H, 2s, $2 \times \text{CH}_3$).

5

Example 64

Preparation of (2'R)-4'-nonyl-4'-demethyl-homoharringtonine :



10

Sodium hydride 60 % (8.9 mg, 0.223 mmol) was added to a solution of homoharringtonine (405 mg, 0.742 mmol) in n-nonanol (4 ml) and the resulting mixture was stirred at ambient temperature for 3 hours under argon. After adjusting to pH 1.3 by addition of hydrochloric acid 0.1N (13 ml), the aqueous layer was washed with petroleum ether (8 ml) and the resulting organic layer was extracted with hydrochloric acid 0.1 N (5 ml). This was repeated an other time. The combined aqueous layers were washed with ether (8 ml) then were alkalinized to pH 9.6 with ammonia 25% (fifteen drops) and were extracted with dichloromethane (6 x 8 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (400 mg crude, 82%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (135 g), buffer pH 3 / methanol, 20:80). After removal of methanol in vacuo the resulting aqueous layer was alkalinized to pH 9.7 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (256 mg; 52%). The product thus obtained showed the following characteristics:

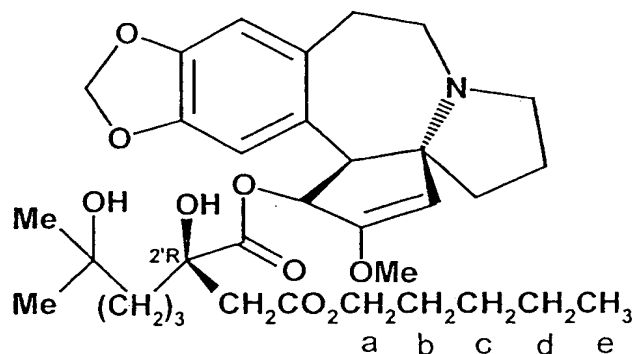
¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.54 (1H, s, H-14), 5.98 (1H, d, J_{3,4} = 9.8, H-3), 5.86 (2H, s, OCH₂O), 5.05 (1H, s, H-1), 4.00 and 3.91 (2H, 2m, CH₂-a), 3.78 (1H, d, J_{4,3} = 9.8, H-4), 3.68 (3H, s, OCH₃), 3.52 (1H, s, 2'-OH), 3.10 (2H, m, H-11β + H-8α), 2.95 (1H, m, H-10α), 2.60 (2H, m, H-8β + H-10β), 2.38 (1H, dd, J = 14.1 and 6.7, H-11α), 2.24 and 1.92 (2H, 2d, J_{AB} = 16.3, CH₂CO₂), 2.03 (1H, m, H-6_A), 1.92 (1H, m, H-6_B), 1.77 (2H, m, CH₂-7), 1.56 (2H, m, CH₂-b), 1.50 - 1.22 (16H, m, CH₂-c,d,e,f,g,h and 3×CH₂), 1.19 (6H, s, 2 × CH₃), 0.88 (3H, t, J = 6.8, CH₃-i).

10

Example 65

Preparation of (2'R)-4'-pentyl-4'-demethyl-homoharringtonine:



15

Sodium hydride 60 % (10.0 mg, 0.250 mmol) was added to a solution of homoharringtonine (416 mg, 0.762 mmol) in n-pentanol (4.2 ml) and the resulting mixture was stirred at ambient temperature for 2 hours under argon. After adjusting to pH 1.8 by addition of hydrochloric acid 0.1N (14 ml), the aqueous layer was washed with ether (3 x 8 ml). The resulting aqueous layer was alkalinized with ammonia 25% (pH = 9.5) and was extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness (339 mg crude, 74%). The crude product thus obtained was purified by phase-reversed chromatography (octadecylsilane 12 μm (130 g), buffer pH 3 / methanol, 40:60). After removal of methanol *in vacuo* the resulting aqueous layer was alkalinized to pH 9.7 with ammonia 25% and extracted with dichloromethane (6 x 10 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to provide the expected compound (274 mg; 60%). The product thus obtained showed the following characteristics:

25

¹H NMR 400 MHz (CDCl₃) (δ ppm, J Hz):

6.62 (1H, s, H-17), 6.55 (1H, s, H-14), (1H, d, J_{3,4} = 9.7, H-3), 5.86 (2H, s, OCH₂O), 5.05 (1H, s, H-1), 4.00 and 3.92 (2H, 2m, CH₂-a), 3.78 (1H, d, J₄₋₃ = 9.2, H-4), 3.68 (3H, s, OCH₃), 3.53 (1H, s, 2'-OH), 3.12 (2H, m, H-11β + H-8α), 2.96 (1H, m, H-10α), 2.61 (2H, m, H-8β + H-10β), 2.41 (1H, m, H-11α), 2.25 and 1.95 (2H, 2d, J_{AB} = 16.2, CH₂CO₂), 2.03 (1H, m, H-6_A), 1.92 (1H, m, H-6_B), 1.78 (2H, m, CH₂-7), 1.57 (2H, m, CH₂-b), 1.50 - 1.22 (10H, m, CH₂-c,d and 3×CH₂), 1.19 (6H, s, 2 x CH₃), 0.90 (3H, t, J = 6.9, CH₃-e)

Biological data

1- Materials and methods

Structural analogues of harringtonines described in this invention were tested on K562 cell line, derived from chronic myeloid leukemia cells in blastic transformation (bcr-abl positive). The cell line was purchased from ATCC (American Tissue Culture Collection) and grown in RPMI medium supplemented with 10% heat-inactivated fetal calf serum, 2 mmol/L glutamine, 50 IU/mol penicillin and 50 IU/mol streptomycin. All tested products were initially dissolved in 2N HCl (pH=2), supplemented with ultrasound treatment during 1h. Working concentrations were made by dilution in culture medium (pH around 7). Cells in exponential growth phase were placed into 96-microwell plates in concentration 3x10⁴/mL (total volume 200 μL/well) and incubated with drugs for 72h at 37°C in 5% CO₂ humidified atmosphere. Following incubation, 20 μL of MTT solution (Sigma, St. Louis, MO) was added to each well. During the following 6h of incubation at 37°C, the purple formazan product was formed by conversion of the yellow MTT salt in the mitochondria of the viable cells. The resulting precipitate was dissolved in DMSO and the amount of converted MTT was quantified in an ELISA reader (MR 5000, Dynatech). Each product was tested in triplicate (3x8 wells). Every test contained at least one plate with HHT as control, added in the same concentration as the tested products.

2- Results

The following table represents the results of some examples of the compounds according to the present invention in K562 cell line compared to the homoharringtonine, the harringtonine and the cephalotaxine.

NAME	EXAMPLE. #	IC ₅₀
O-HEXADIENYL-DMHO ¹	43	3.5
O-HEXYL-DMHO	54	5
O-METALLYL-DMHO	41	8.5
O-HEXENYL-DMHO	53	8.5
O-HEXADIENYL-DMHD	57	9
O-BUTYNYL-DMHO	42	10.5
O-CROTYL-DMHO	37	12.5
O-BUTYL-DMHO	50	13
O-CROTYL-DMHD ²	56	13.5
FLUORODESOXYHARRINGTONINE	59	13.5
O-CROTYL-DMHA ³	55	14
HOMOHARRINGTONINE		14
O-ALLYL-DMHO	40	14.5
DESHYDRO-HHT	61	17.5
THIOTERBUTYL-DMHO	36	20
O-PROPYL-DMHO	51	22.5
O-ISOBUTYL-DMHO	52	24
O-SENECYL-DMHO	39	28
HARRINGTONINE (HHT) ⁴		30
O-ETHYL-DMHO	25	41
THIOISOPROPYL-DMHO	34	50
THIOMETHYL-DMHO	30	50
O-METHYLCYCLOPROPYL-DMHO	49	70
O-ISOPROPYL-DMHO	27	80
THIOETHYL-DMHO	32	80
O-TRIFLUOROETHYL-DMHO	48	100
CEPHALOTAXINE (CTX) ⁵		2000

5

¹DMHO means 4'-demethyl-homoharringtonine

²DMHD means 4'-demethyl-4"-hydroxydrupangtonine

³DMHA means 4'-demethyl-harringtonine

⁴HHT means homoharringtonine (natural or semi-synthetic source)

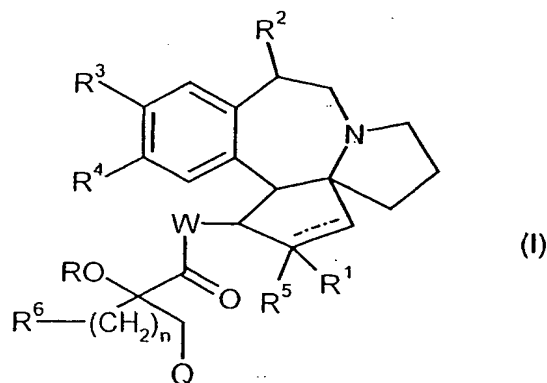
10 ⁵CTX means cephalotaxines (natural source)

The same method as above was used to test the O-hexadienyl-DMHO (example 43) on K562_{MRP}, a subline of K562 line exhibiting a strong resistance to

50 ng/mL of homoharringtonine. The IC_{50} of the O-hexadienyl-DMHO (example 43) was 16 ng/mL, i.e. a value not significantly different from homoharringtonine itself in non resistant version of K562 line (cf. above table)

CLAIMS

1. A compound of formula (I)



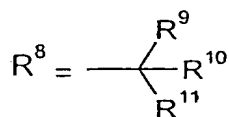
5 wherein

- W represents O or NH,
- Q represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s),
- 10 • R¹ is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or null and R² is H or OH, or R¹, R² form together -O-,
- R³ = R⁴ = OMe or R³ and R⁴ form together -OCH₂O-,
- R is H, C₁-C₃₀alkyl or O-protecting group and R⁶ represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms including or not heteroatom(s), or R and R⁶ form together -CMe₂-,
- 15 • n is 0 to 8,
- R⁵ is H, OH, OMe, O-(C₁-C₃₀)-alkyl, O-aryl-(C₁-C₃₀)-alkyl, O-(C₂-C₃₀)-alkenyl, O-(C₃-C₃₀)-cycloalkyl or O-aryl,
- 20 • the dotted line is null or forms a double bond depending on the meaning of R¹,

except for compounds where

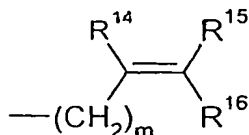
- W represents O, the dotted line forms a double bond, R¹ is null, R² is H, R³ and R⁴ represent -O-CH₂-O-, R⁵ is OMe, Q = CO₂R⁷ and
- 25

- 1°) $R = H$, $R^6 = -(C-OH)Me_2$, $n = 2$ or 3 , $R^7 = Me$ or H ,
 2°) $R = H$, $R^6 = -(C-H)Me_2$, $n = 2$ to 4 , $R^7 = Me$,
 3°) $R = H$, $R^6 = -(C-H)Me_2$, $n = 1$ or 2 , $R^7 = H$,
 4°) $R = H$, $R^6 = Ph$, $n = 1$ to 3 , $R^7 = Me$,
 5 5°) $R = H$, $R^6 = -CH=CH-Ph$, $n = 0$, $R^7 = Me$,
 6°) $R = H$, $R^6 = CH_3$, $n = 4$, $R^7 = Me$,
 7°) R and R^6 form together $-CMe_2-$, $n = 2$ or 3 , $R^7 = Me$,
- W represents O, the dotted line forms a double bond, R^1 is null, R^2 is OH, R^3 and R^4 represent $-O-CH_2-O-$, R^5 is OMe, and
- 10 $R = H$, $R^6 = -(C-H)Me_2$, $n = 2$ or 3 , $R^7 = Me$
- W represents O, the dotted line is null, R^1 and R^2 represent $-O-$, R^3 and R^4 represent $-O-CH_2-O-$, R^5 is OMe, and
- $R = H$, $R^6 = -(C-H)Me_2$, $n = 2$, $R^7 = Me$
2. A compound of formula (I) according to claim 1 wherein
- 15 • $Q = COZ-R^8$,
- $Z = O$, S , or NH , and



or $Z-R^8$ is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10} ,

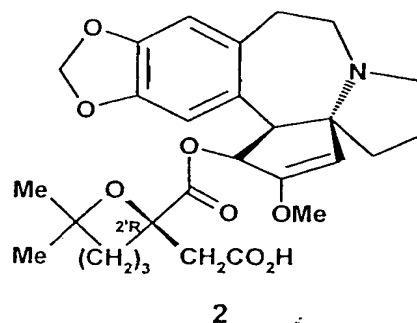
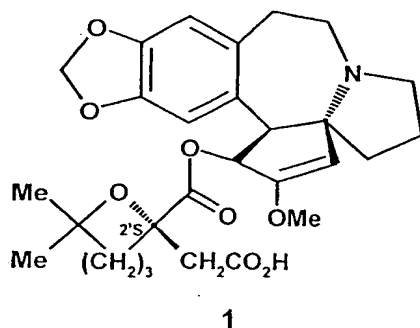
- R^9 , R^{10} , R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-
- 20 (C_1-C_{30}) -alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30} alkylamino- (C_1-C_{30}) -alkyl, C_1-C_{30} dialkylamino- (C_1-C_{30}) -alkyl, or amino- (C_1-C_{30}) -alkyl, or

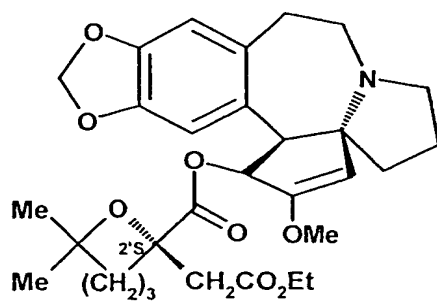


- where R^{14} , R^{15} , R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl,
- 25 aryl, aryl- (C_1-C_{30}) -alkyl, C_2-C_{30} alkenyl or C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, m is 0 to 4,
- each of these groups including or not heteroatom(s).

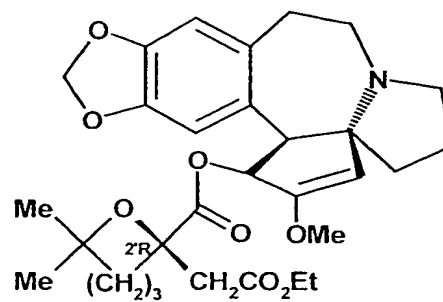
3. A compound of formula (I) according to claim 2 wherein

- $R^6 = -(C-Y)Me_2$, $-CH=CMe_2$, or an aryl group
or R and R^6 form together $-CMe_2-$,
Y = H, OH or halogen.
- 4. A compound of formula (I) according to claim 3 wherein
- 5 • the dotted line forms a double bond
- R^1 is null
- R^2 is H
- R^3 and R^4 represent $-O-CH_2-O-$
- R^5 is OMe.
- 10 5. A compound of formula (I) according to claim 3 wherein
- the dotted line is null
- R^1 and R^2 represent $-O-$
- R^3 and R^4 represent $-O-CH_2-O-$
- R^5 is OMe.
- 15 6. A compound of formula (I) according to claim 4 or 5 wherein
- $n = 1$ to 3.
- 7. A compounds of formula (I) according to anyone of the claims 1 to 6
wherein W represents O.
- 8. A compound of formula (I) according to claim 7 wherein it is selected from
- 20 the group consisting of the following compounds 1 to 65 :

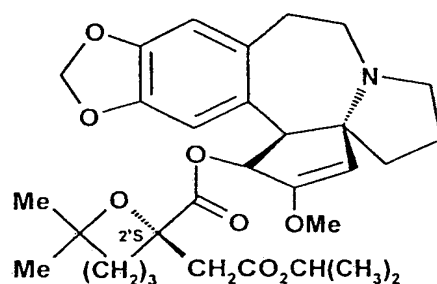




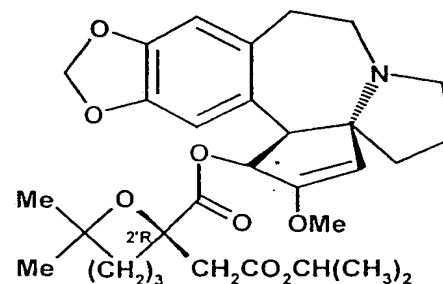
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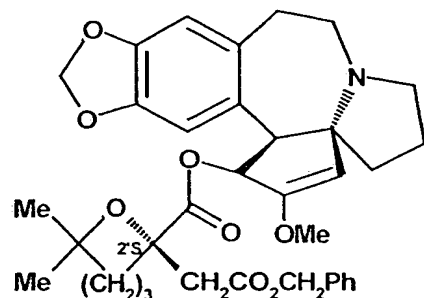


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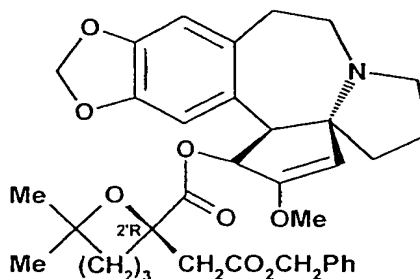


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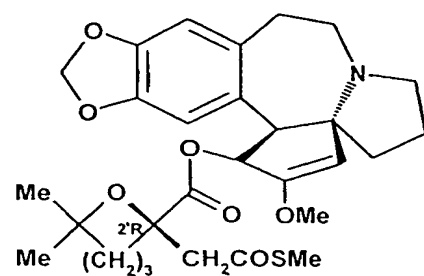
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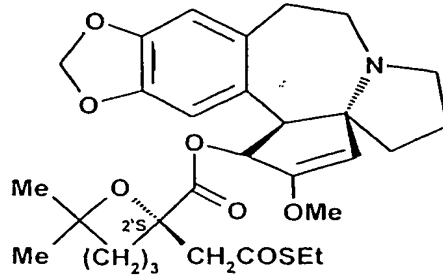
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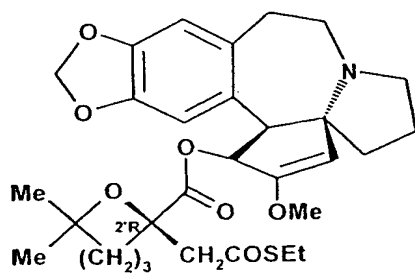


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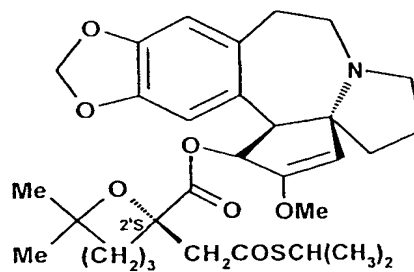


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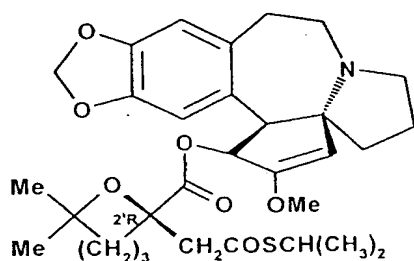
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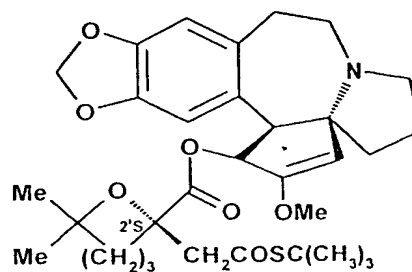
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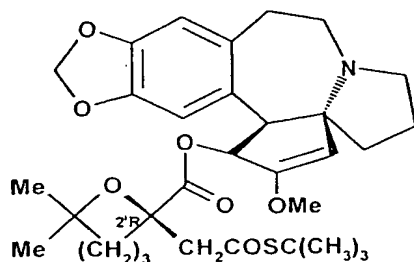
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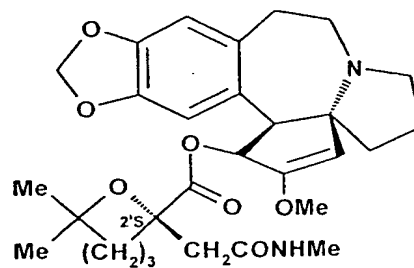
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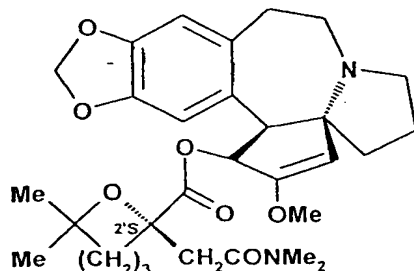
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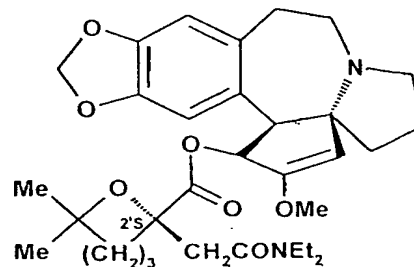
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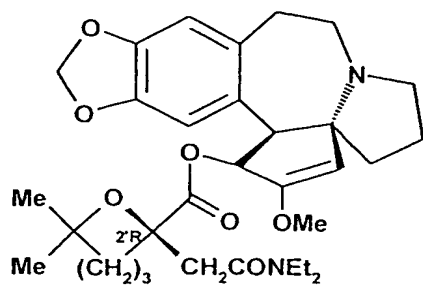
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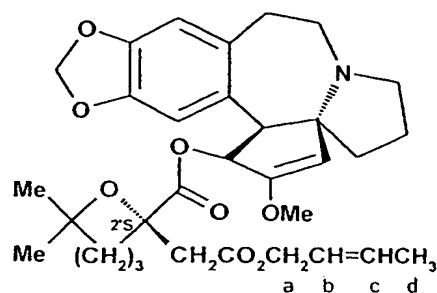
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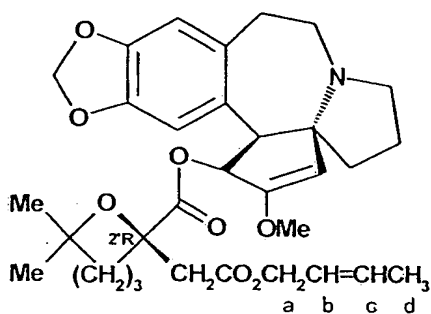
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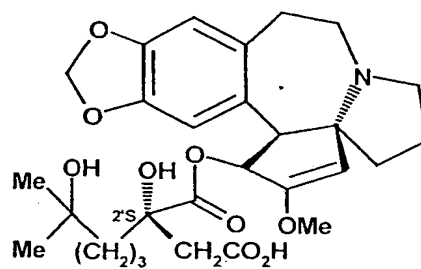
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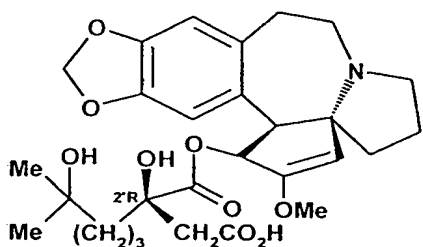
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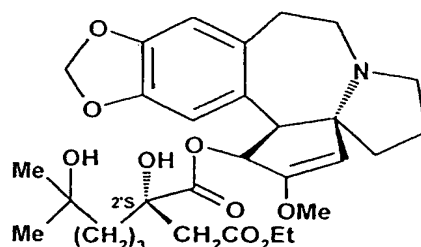
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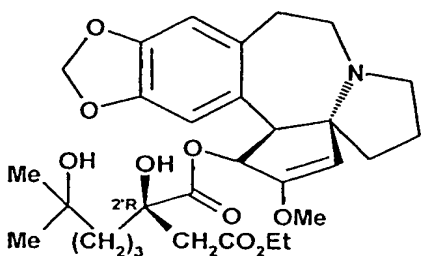
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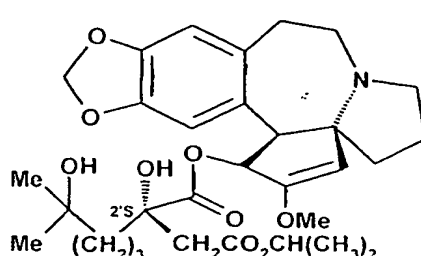
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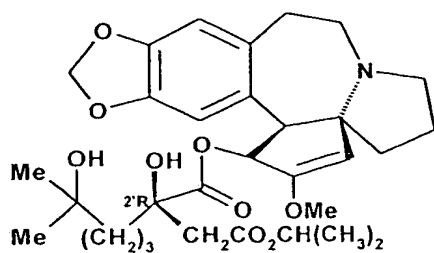
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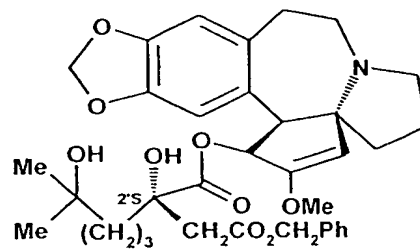
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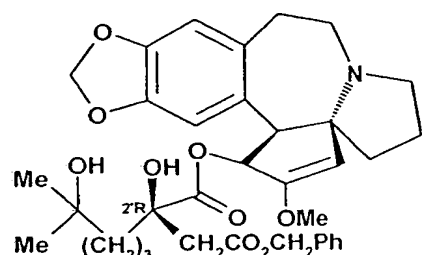
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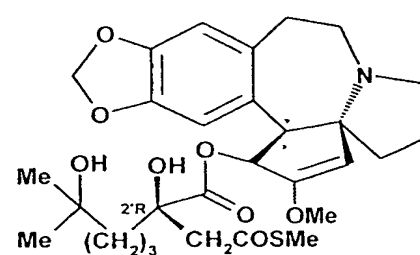
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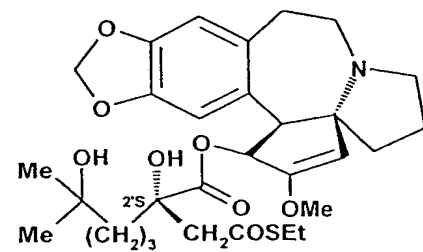
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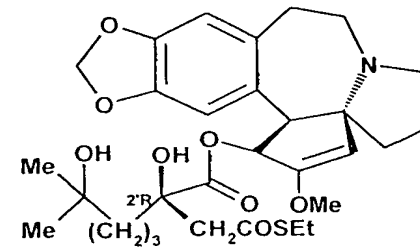
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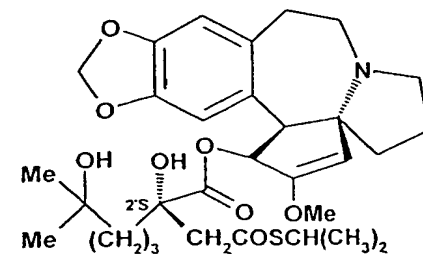
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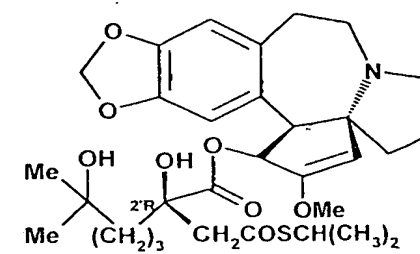
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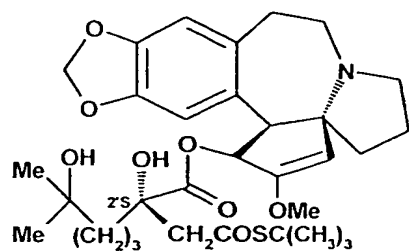
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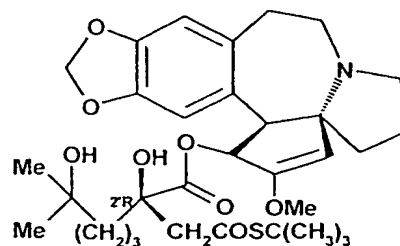
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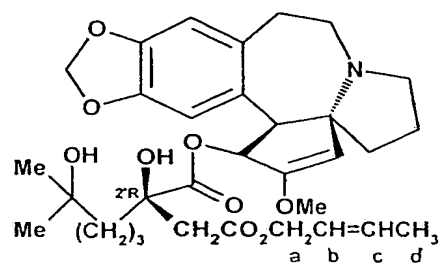
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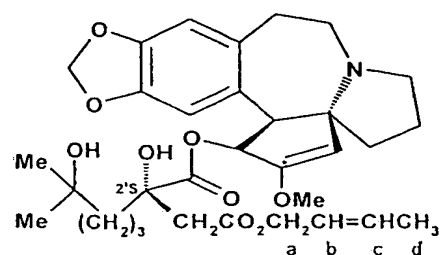
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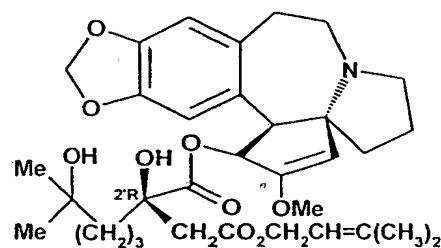
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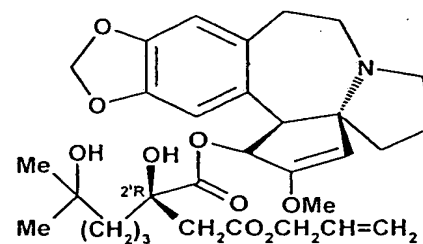
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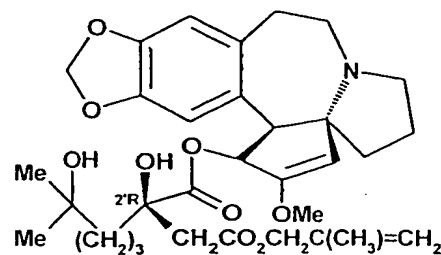
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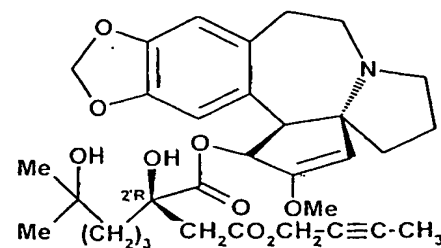
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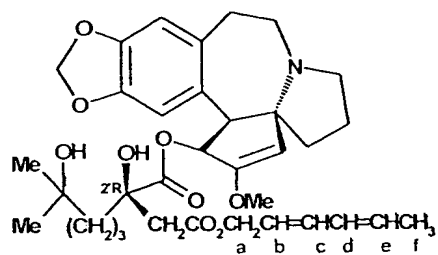
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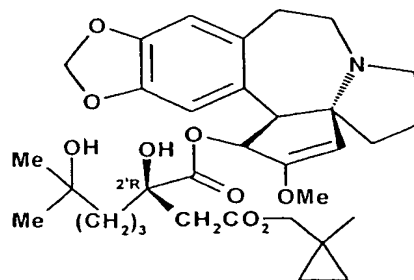
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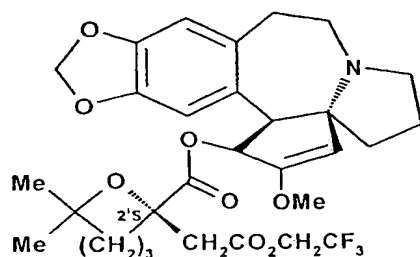
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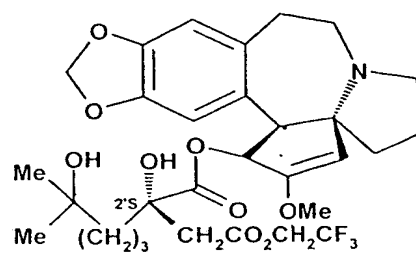
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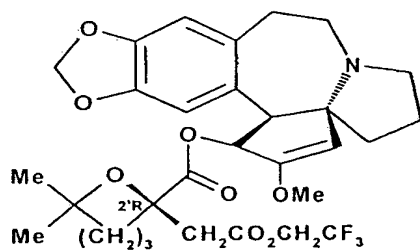
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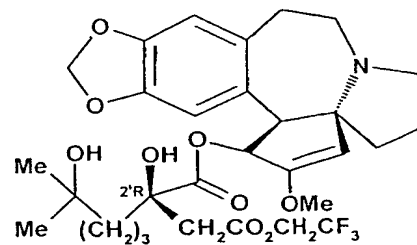
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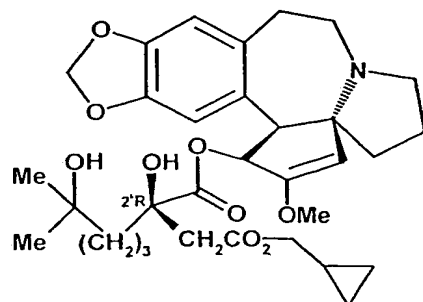
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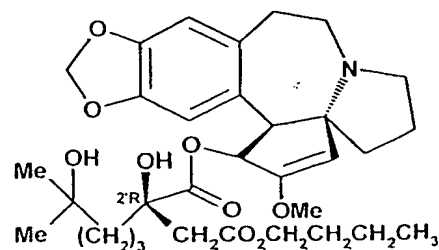
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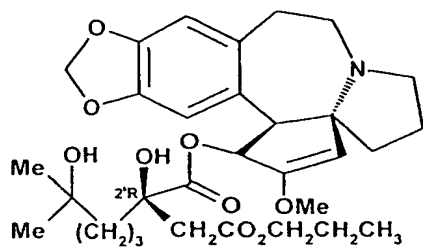
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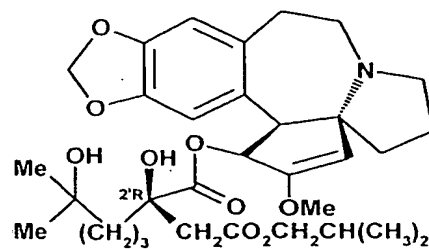
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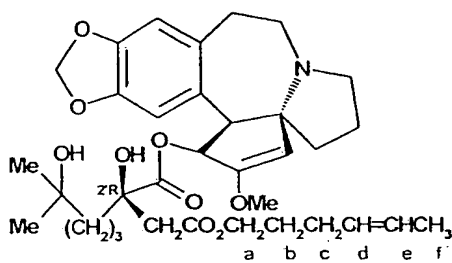
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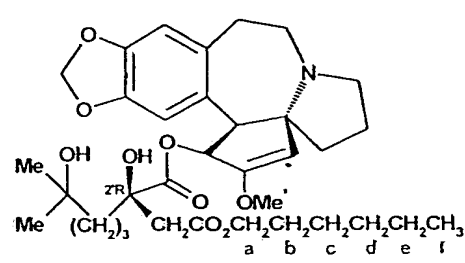
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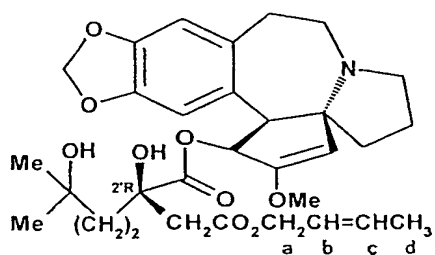
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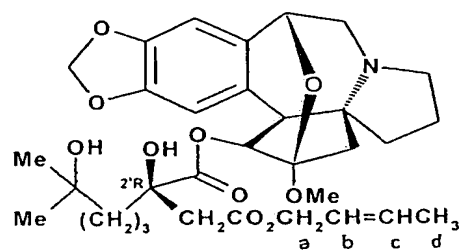
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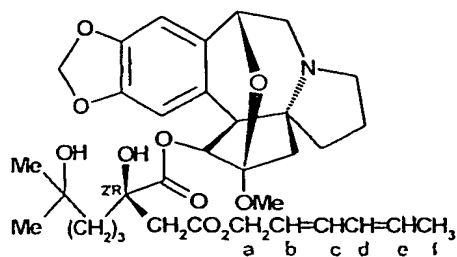
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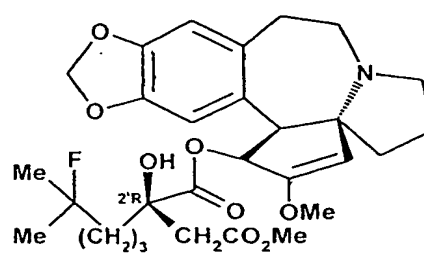
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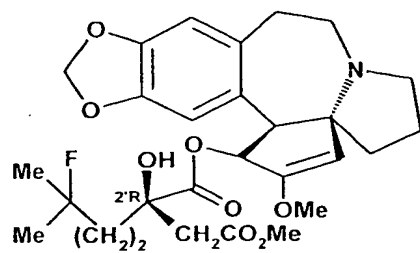
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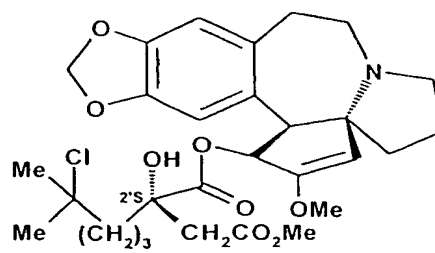
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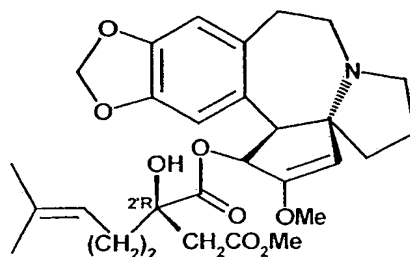
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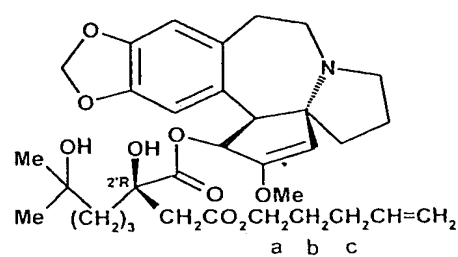
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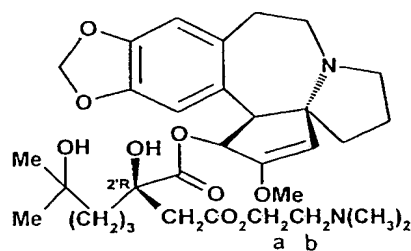
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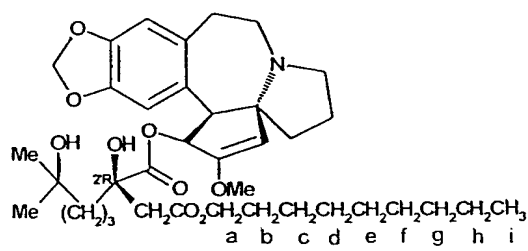
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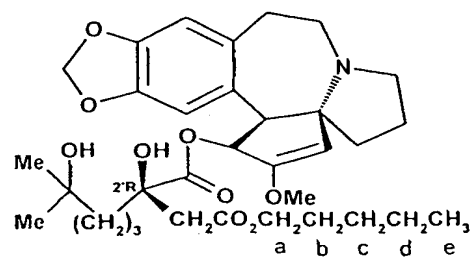


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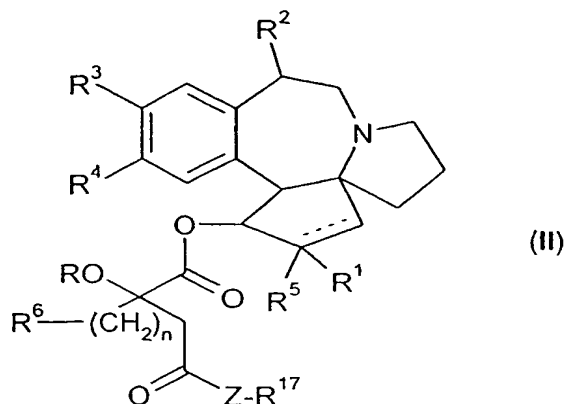
and



65.

9. A process for preparing a compound of formula (I) according to claim 1 to 8 in the case where W represents O, $Q = \text{COZ-R}^8$ and Z and R^8 are defined as in claim 2 comprising the following steps i) then ii),

i) hydrolyzing selectively the compound of formula (II)

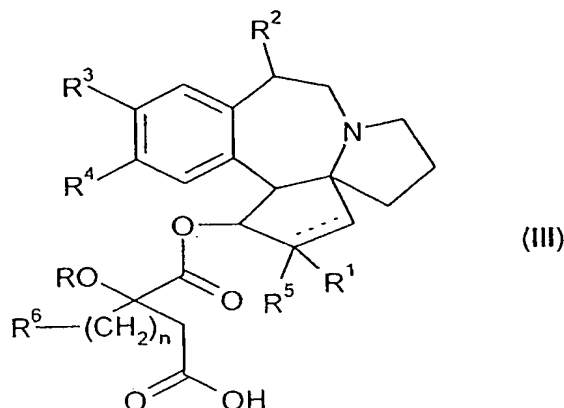


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wherein

- R^1 is H, OH, OMe, O-($\text{C}_1\text{-C}_{30}$)-alkyl, O-aryl-($\text{C}_1\text{-C}_{30}$)-alkyl, O-($\text{C}_2\text{-C}_{30}$)-alkenyl, O-($\text{C}_3\text{-C}_{30}$)-cycloalkyl or null and
- R^2 is H or OH, or R^1 and R^2 form together $-\text{O}-$,
- 10 • $\text{R}^3 = \text{R}^4 = \text{OMe}$ or R^3 and R^4 form together $-\text{OCH}_2\text{O}-$,
- R is H, $\text{C}_1\text{-C}_{30}$ alkyl or O-protecting group and R^6 represents an unbranched or branched, saturated or unsaturated or aromatic, cyclic or acyclic or heterocyclic hydrocarboned radical containing 1 to 30 carbon atoms, including or not heteroatom(s), or R and R^6 form together $-\text{CMe}_2-$
- 15 • n is 0 to 8.
- R^5 is H, OH, OMe, O-($\text{C}_1\text{-C}_{30}$)-alkyl, O-aryl-($\text{C}_1\text{-C}_{30}$)-alkyl, O-($\text{C}_2\text{-C}_{30}$)-alkenyl, O-($\text{C}_3\text{-C}_{30}$)-cycloalkyl or O-aryl,
- the dotted line is null or forms a double bond depending on the meaning of R^1
- 20 • Z= O or S, and
- R^{17} is $\text{C}_1\text{-C}_{30}$ alkyl, $\text{C}_2\text{-C}_{30}$ alkenyl, $\text{C}_3\text{-C}_{30}$ cycloalkyl, $\text{C}_2\text{-C}_{30}$ alkynyl, aryl-($\text{C}_1\text{-C}_{30}$)-alkyl or aryl, advantageously methyl or ethyl

with an agent such as mineral hydroxide, advantageously lithium, potassium or sodium hydroxide, in hydro-organic solvent mixture to give as reaction product, amphoteric acid of formula (III)



- 5 wherein R^1 to R^5 , R and R^6 are defined as above,
- ii) performing the esterification of the above obtained amphoteric acid of formula (III) with an esterification agent and a compound of formula R^8-ZH , R^8 and Z being defined as in claim 2
- and wherein the steps i) and ii) are carried out successively or simultaneously.
- 10 10. The process as described in claim 9 wherein the esterification agent is a lewis acid or a protonic acid.
11. The process as described in claims 9 and 10 wherein the amphoteric acid of formula (III) is activated with an imide or by formation of a mixte anhydride or an acid chloride.
- 15 12. The process as described in claim 11 wherein the imide is dicyclohexylcarbodi-imide or diisopropylcarbodiimide.
13. The process as described in claim 11 wherein the mixte anhydride is formed with 2,4,6-trichlorobenzoic acid by contact with 2,4,6-trichlorobenzoyl chloride in the presence of a base.
- 20 14. The process as described in claim 9 wherein the steps i) and ii) are carried out simultaneously, without isolation of the amphoteric acid of formula (III), via a reaction of transesterification performed in presence of an acidic or basic catalyst.
15. The process as described in claim 14 wherein the catalyst is a base,
- 25 such as an alkaline hydride.

16. The process as described in claim 14 wherein the catalyst is a lewis acid or a protonic acid.

17. The process as described in claims 9 to 16 wherein Z is O and R¹⁷ is methyl.

5 18. A pharmaceutical composition which comprises a therapeutically effective amount of at least one compound of anyone of claims 1 to 8 associated with one or more pharmaceutically acceptable carriers.

19. The use of at least one compound of anyone of claims 1 to 8 or of a pharmaceutical composition of claim 18 as chemotherapeutic agent.

10 20. The use of at least one compound of anyone of claims 1 to 8 or of a pharmaceutical composition of claim 18 as enhancer of other chemotherapeutic agents.

21. The use of at least one compound of anyone of claims 1 to 8 or of a pharmaceutical composition of claim 18 for inhibiting tumors growth.

15 22. The use of at least one compound of anyone of claims 1 to 8 or of a pharmaceutical composition of claim 18 for inhibiting mammalian parasites.

23. The use according to anyone of the claims 19 to 22 on leukemic cell lines exhibiting resistance to other agents in particular harringtonine.

20 24. The use of at least one compound of anyone of claims 1 to 8 or of a pharmaceutical composition of claim 18 as reversal agent, in particular of harringtonine.

25. A method for treating mammalian tumors which comprises administering to a mammal a therapeutically effective amount of at least one compound of anyone of claims 1 to 8 or a pharmaceutical composition of claim 18.

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/IB 00/01593

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/20 C07D487/20 C07D498/22 C07D498/20 A61K31/55
A61P35/02 //(C07D491/20, 317:00, 223:00, 209:00), (C07D487/20,
223:00, 209:00), (C07D498/22, 317:00, 313:00, 267:00, 209:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 48894 A (ONCOPHARM CORPORATION, USA) 30 September 1999 (1999-09-30) page 103 -page 104; examples 23,24	1-25
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHENG, JIACHONG ET AL: "Stereospecific synthesis of deoxyharringtonine and homoharringtonine" retrieved from STN Database accession no. 103:160738 XP002163590 abstract; figure 313 & YAOXUE XUEBAO (1984), 19(3), 178-83 , ----- -/--	1-25

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

22 March 2001

Date of mailing of the International search report

12/04/2001

Name and mailing address of the ISA

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Authorized officer

Paisdor, B

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/IB 00/01593

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D498/20, 313:00, 267:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORITA, HIROSHI ET AL: "Cephalezomines A-F, potent cytotoxic alkaloids from Cephalotaxus harringtonia var. nana" TETRAHEDRON (2000), 56(19), 2929-2934 , XP004198001 compounds 1 and 2 page 2930 ---	1-25
X	TAKANO, ICHIRO ET AL: "New cephalotaxus alkaloids from Cephalotaxus harringtonia var. drupacea" J. NAT. PROD. (1996), 59(10), 965-967 , XP002163587 the whole document --- -/--	1-25

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INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/IB 00/01593

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WANG, YONGKENG ET AL: "Synthesis of homoharringtonine and separation of its stereomers" retrieved from STN Database accession no. 103:71569 XP002163591 abstract; figure 315 & HUAXUE XUEBAO (1985), 43(2), 161-7 ,</p>	1-25
X	<p>HIRANUMA, SAYOKO ET AL: "Studies in Cephalotaxus alkaloids. Stereospecific total synthesis of homoharringtonine" J. ORG. CHEM. (1983), 48(26), 5321-6 , XP002087582 compounds 13a and 13b page 5322</p>	1-25
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CONG, PUZHU: "Mass spectroscopic study of cephalotaxine alkaloids" retrieved from STN Database accession no. 99:54042 XP002163592 abstract; figure 318 & YAOXUE XUEBAO (1983), 18(3), 215-26 ,</p>	1-25
X	<p>HIRANUMA, S. ET AL: "Synthesis of homoharringtonine and its derivative by partial esterification of cephalotaxine" TETRAHEDRON LETT. (1982), 23(34), 3431-4, XP002163588 compound 4 page 3433</p>	1-25
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LI, YULIN ET AL: "New synthetic method for harringtonine" retrieved from STN Database accession no. 98:16906 XP002163593 abstract; figure 324 & LANZHOU DAXUE XUEBAO, ZIRAN KEXUEBAN (1982), 18(3), 126 ,</p>	1-25

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INTERNATIONAL SEARCH REPORT

Inter Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LI, SHU-WEN ET AL: "A study on the deoxyharringtonine and its analogs" retrieved from STN Database accession no. 85:108857 XP002163594 abstract; figure 328 & HUA HSUEH HSUEH PAO (1975), 33(1), 75-8</p>	1-25
X	<p>----- MIKOLAJCZAK, K. L. ET AL: "Partial synthesis of harringtonine analogs" J. PHARM. SCI. (1974), 63(8), 1280-3 , XP002163589 compound III page 1280 -----</p>	1-25

INTERNATIONAL SEARCH REPORT

Inte Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9948894 A	30-09-1999	FR 2776292 A	24-09-1999
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